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(54) Title: MAMMALIAN GENES; DENDRITIC CELL PROSTAGLANDIN–LIKE TRANSPONDER (DC–PGT), HDTEA84, HSLJD37R AND RANKL, HCC5 CHEMOKINE, DEUBIQUITINATING 11 AND 12 (DUB11, DUB12), MD–1, MD2 AND CYCLIN E2, RELATED REAGENTS AND METHODS

(57) Abstract

Purified genes from a mammal, reagents related thereto including purified proteins, specific antibodies, and nucleic acids encoding the polypeptides are provided. Methods of using said reagents and diagnostic kits are also provided. Characterization of genes and products relating to DC–PGT (Dendritic cell prostaglandin–like transporter), HDTEA84, HSLJD37R and RANKL (related to TNF receptor family), HCC5 chemokine, Dub 11 and Dub 12 (Deubiquitinating 11 and 12), MD–1 and MD–2 (proteins which exhibit properties of ligands for proteins exhibiting a leucine–rich protein motif (LRR)) and cyclin E2.

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MAMMALIAN GENES: DENDRITIC CELL PROSTAGLANDIN-LIKE TRANSPONDER (DC-PGT), HDTEA84, HSLJD37R AND RANKL, HCC5 CHEMOKINE, DEUBIQUITINATING 11 AND 12 (DUB11, DUB12), MD-1, MD2 AND CYCLIN E2, RELATED REAGENTS AND METHODS

FIELD OF THE INVENTION

The present invention pertains to compositions related to proteins which: function in cellular physiology, development, and differentiation of mammalian cells; exhibit sequence similarity to TNF receptors which function in controlling activation and expansion of mammalian cells, e.g., cells of a mammalian immune system; or function in controlling the cell cycle and growth. In particular, it provides purified genes, proteins, antibodies, and related reagents useful, e.g., to separate or identify particular cell types, or to regulate activation, development, differentiation, and function of various cell types, including hematopoietic cells; which exhibit high structural similarity to proteins that exhibit the biological capacity to serve as a carrier mediated transporters of charged organic anions across cellular membranes, which typically can be used in prostaglandin and thromboxane physiology, e.g., transportation, influx, efflux, clearance, or degradation; which regulate or evidence development, differentiation, and function of various cell types, including hematopoietic cells; or to regulate cell division and proliferation of various cell types, including tumor cells.

BACKGROUND OF THE INVENTION

Prostaglandins (PGs) and thromboxanes (TXs) play widespread physiological, and therapeutic roles in health and disease such as glaucoma; pregnancy, labor, delivery, and abortion; gastric protection and peptic ulcer formation; intestinal fluid secretion; liver protection and damage; airway resistance and asthma; blood pressure control; and modulation of inflammatory cells.

PGs are charged anions at physiological pH that diffuse poorly across biological membranes. This limited simple diffusion appears to be augmented by carrier mediated transport in many diverse tissues such as the lung, choroid plexus, liver, anterior chamber of the eye, vagina, uterus, and placenta.

Understanding the role of prostaglandins in the development and functioning of the immune system is presently incomplete. Specifically, the influence of prostaglandins (PGs) on antigen presenting cells (APCs) of the immune system (e.g., dendritic cells) is, as yet, poorly understood.

Dendritic cells (DCs) are the most potent of antigen presenting cells. See, e.g., Paul (ed. 1993) Fundamental Immunology 3d ed., Raven Press, NY. DCs are highly responsive to inflammatory stimuli such as bacterial lipopolysaccharides (LPS) and cytokines such as tumor necrosis factor alpha (TNFα). The presence of cytokines and LPS can induce a series of phenotypic and functional changes in DC that are collectively referred to as maturation. See, e.g., Banchereau and Schmitt Dendritic Cells in Fundamental and Clinical Immunology Plenum Press, NY.

Maturational changes in DCs include, e.g., silencing of antigen uptake by endocytosis, upregulation of surface molecules related to T cell activation, and active production of a number of cytokines including TNFα and IL-12. Upon local accumulation of TNFα, DCs migrate to the T cell areas of secondary lymphoid organs to activate antigen specific T cells.

Recent data indicate that DCs secrete PGs. See, e.g., Cormann, et al. (1986) Ann. Inst. Pasteur 137:369-382. Furthermore, PGE_2 has been shown to have an influence on DC maturity and the production of cytokines by DCs. Seem e.g., Kalinski, et al. (1997) J. Immunol. 159:28-35; Kuhn, et al. (1997) Eur. J. Immunol. 27:3135-3142; and Rieser, et al. (1997) J. Exp. Med. 186:1603-1608.

Currently, a need exists to understand the manner in which PGs influence cells of the immune system. It seems likely that PGs, like cytokines, effect immune system development and activation. The present invention contributes to satisfying that need and is directed generally to a novel mammalian gene encoding a prostaglandin-like transporter (PGT).

In other aspects, the activation of resting T cells is critical to most immune responses and allows these cells to exert

their regulatory or effector capabilities. See, e.g., Paul (ed. 1993) Fundamental Immunology 3d ed., Raven Press, N.Y. Increased adhesion between T cells and antigen presenting cells (APC) or other forms of primary stimuli, e.g., immobilized monoclonal antibodies (mAb), can potentiate the T-cell receptor signals. T-cell activation and T cell expansion depends upon engagement of the T-cell receptor (TCR) and co-stimulatory signals provided by accessory cells. See, e.g., Jenkins and Johnson (1993) Curr. Opin. Immunol. 5:361-367; Bierer and Hahn (1993) Semin. Immunol. 5:249-261; June, et al. (1990) Immunol. Today 11:211-216; and Jenkins (1994) Immunity 1:443-446. A major, and well-studied, co-stimulatory interaction for T cells involves either CD28 or CTLA-4 on T cells with either B7 or B70 (Jenkins (1994) Immunity 1:443-446). Recent studies on CD28 deficient mice (Shahinian, et al. (1993) Science 261:609-612; Green, et al. (1994) Immunity 1:501-508) and CTLA-4 immunoglobulin expressing transgenic mice (Ronchese, et al. (1994) J. Exp. Med. 179:809-817) have revealed deficiencies in some T-cell responses though these mice have normal primary immune responses and normal CTL responses to lymphocytic choriomeningitis virus and vesicular stomatitis virus. As a result, both these studies conclude that other co-stimulatory molecules must be supporting T-cell function. However, identification of these molecules which mediate distinct costimulatory signals has been difficult.

Tumor Necrosis Factor (TNF) is the prototypic member of an emerging family of cytokines that function as prominent mediators of immune regulation and the inflammatory response. These ligands are typically type II membrane proteins, with homology at the carboxy terminus. A proteolytic processed soluble protein often is produced. See, e.g., Smith, et al. (1994) Cell 76-959-962; Armitage (1994) Current Opinion in Immunology 6:407-413; Gruss and Dower (1995) Blood 85:3378-3404; Wiley, et al. (1995) Immunity 3:673-682; and Baker and Reddy (1996) Oncogene 12:1-9. Crucial roles for these family members are evidenced by a number of studies, and they are implicated in regulation of apoptosis, peripheral tolerance, Ig maturation and isotype switching, and

general B cell and T cell functions. See, e.g., Thomson (ed. 1994) The Cytokine Handbook Academic Press, San Diego, CA; Naismith and Sprang (1998) Trends Biochem. Sci. 23:74-79; Lucas, et al. (1997) J. Leukoc. Biol. 61:551-558; Reddi (1997) Cell 89:159-161; Van Deventer (1997) Gut 40:443-448; Jablonska (1997) Postepy. Hig. Med. Dosw. 51:567-575; Hill and Lunec (1996) Mol. Aspects Med. 17:455-509; Aderka (1996) Cytokine Growth Factor Rev. 7:231-240; Lotz, et al. (1996) J. Leukoc. Biol. 60:1-7; and Gruss and Dower (1995) Cytokines Mol. Ther. 1:75-105. These imply fundamental roles in immune and developmental networks relevant to human therapeutic needs. The identification of ligands and cell surface receptors allow determination of pairs, which will be useful in modulating such signal transduction.

The discovery of new cell markers is always potentially useful. Moreover, the inability to modulate activation signals prevents control of inappropriate developmental or physiological responses in the immune system. The present invention provides at least one alternative costimulatory molecule, which will be useful as a marker for cell types, and agonists and antagonists of which will be useful in modulating a plethora of immune conditions or responses.

The circulating component of the mammalian circulatory system comprises various cell types, including red and white blood cells of the erythroid and myeloid cell lineages. See, e.g., Rapaport (1987) Introduction to Hematology (2d ed.) Lippincott, Philadelphia, PA; Jandl (1987) Blood: Textbook of Hematology, Little, Brown and Co., Boston, MA.; and Paul (ed. 1993) Fundamental Immunology (3d ed.) Raven Press, N.Y.

For some time, it has been known that the mammalian immune response is based on a series of complex cellular interactions, called the "immune network." Recent research has provided new insights into the inner workings of this network. While it remains clear that much of the response does, in fact, revolve around the network-like interactions of lymphocytes, macrophages, granulocytes, and other cells, immunologists now generally hold the opinion that soluble proteins, known as lymphokines,

cytokines, or monokines, play a critical role in controlling these cellular interactions. Thus, there is considerable interest in the isolation, characterization, and mechanisms of action of cell modulatory factors, an understanding of which should lead to significant advancements in the diagnosis and therapy of numerous medical abnormalities, e.g., immune system and other disorders.

Lymphokines apparently mediate cellular activities in a variety of ways. They have been shown to support the proliferation, growth, and differentiation of the pluripotential hematopoietic stem cells into vast numbers of progenitors comprising diverse cellular lineages making up a complex immune system. These interactions between the cellular components are necessary for a healthy immune response. These different cellular lineages often respond in a different manner when lymphokines are administered in conjunction with other agents.

The chemokines are a large and diverse superfamily of proteins. The superfamily is subdivided into two classical branches, based upon whether the first two cysteines in the chemokine motif are adjacent (termed the "C-C" branch), or spaced by an intervening residue ("C-X-C"). A more recently identified branch of chemokines lacks two cysteines in the corresponding motif, and is represented by the chemokines known as lymphotactins. Another recently identified branch has three intervening residues between the two cysteines, e.g., CX3C chemokines. See, e.g., Schall and Bacon (1994) Current Opinion in Immunology 6:865-873; and Bacon and Schall (1996) Int. Arch. Allergy & Immunol. 109:97-109.

Because the physiology mediated by these soluble molecules is so important, the discovery of novel chemokines will be important, both in diagnostic and therapeutic contexts.

In addition, while the general importance of the regulation of protein synthesis is universally accepted, the general importance of protein degradation has not been fully appreciated. One mechanism of protein degradation is via ubiquitination signals and degradation pathways. Ubiquitin (Ub) is a highly conserved 76 amino acid polypeptide that plays an important role in the regulation of protein degradation, cell-cycle progression, gene

transcription and signal transduction. The ubiquitination pathway is fine tuned and controlled, in part, by deubiquitination enzymes, which remove ubiquitin from proteins. Misregulation of the ubiquitination pathway may contribute problems in the protein quantity regulation, which may be associated, e.g., with malignant transformation, and oncogenesis through oncogenic counterparts of normally processed ubiquitinated proteins. Other clinical problems will often result from excessive or insufficient protein levels. Therefore, understanding the ubiquitination roles, e.g., in immune function, will increase our understanding of cell biology, which should have relevance, e.g., to malignant transformation.

Furthermore, growth of normal resting B cells (also referred to as "B lymphocytes") involves two distinct steps. First, the resting cells are activated to pass from the G_0 to G_1 phase of the cell cycle. See, e.g., Alberts, et al. (eds. 1989) Molecular Biology of the Cell Garland Publ., NY; and Darnell, et al. (1990) Molecular Cell Biology Freeman, NY. Next, the activated cells are induced to proliferate. See, e.g., Paul, ed. (1989) Fundamental Immunology, 2nd ed., Raven Press, NY; and the third edition. Several factors have been identified that induce growth of B cells, including interleukin-1 (IL-1), IL-2, IL-4, IL-10, and IL-13. In addition, antibodies against certain B cell surface molecules have been demonstrated to promote B cell proliferation. T cells (also referred to as "T lymphocytes") are also induced to proliferate by certain factors, which include phytohemagglutinin, anti-T cell receptor monoclonal antibodies, anti-CD3 monoclonal antibodies, and other agents.

B7 (CD80) and B70 (CD86) are the second "group" of molecules which strongly mediate B and T cell interaction. These molecules, on B cells, interact with their ligands CD28 and CTLA-4 on T cells. These interactions are major co-stimulatory signals for activation of both B and T cells.

During the last 15 years, it has become apparent that B7 (CD80) and B70 (CD86) play fundamental functions in T cell and B cell activation Numerous in vitro and in vivo experiments have demonstrated that these two pairs of molecules represent important

targets for immunosuppression. See, e.g., Banchereau, et al. (1994) Ann. Rev. Immunol. 12:881-922; van Kooten, et al. (1996) Adv. Immunol. 61:1-77; Linsley and Ledbetter (1993) Ann. Rev. Immunol. 11:191-212).

In 1995, another molecule called RP105 was cloned from mouse splenic cells. See Miyake, et al (1995) J. Immunol. 154:3333-3340. Monoclonal antibodies against RP105 also induce strong proliferation of mouse B cells and protects mouse B cells from irradiation-induced apoptosis in a similar fashion to anti-CD40 antibody or CD40-ligand. See Miyake, et al. (1994) J. Exp. Med. 180:1217-1224.

The RP105 molecule and its ligand MD-1 may be an additional pair of molecules that play key roles in the activation of T cells and B cells. See Miyake, et al. (1998) J. Immunol. 161:1349-1353; and Chan, et al., (1998) J. Exp. Med. 188:93-101 However, the human sequence of MD-1, has remained undetermined. The present invention provides this and also provides a previously undescribed second human homolog of mouse MD-1, (i.e., MD-2).

Many factors have been identified which influence the differentiation process of precursor cells, or regulate the physiology or migration properties of specific cell types. These observations indicate that other factors exist whose functions in immune function were heretofore unrecognized. These factors provide for biological activities whose spectra of effects may be distinct from known differentiation or activation factors. The absence of knowledge about the structural, biological, and physiological properties of the regulatory factors which regulate cell physiology in vivo prevents the modulation of the effects of such factors. Thus, medical conditions where regulation of the development or physiology of relevant cells is required remains unmanageable.

Thus, significant therapeutic needs exist in the areas of cytokine regulation of physiology, protein degradation, and B cell signaling. The present invention provides important insights and developments in these areas.

Cancer can occur in many tissues of the body. It results from a change in certain cells that causes them to evade the

normal growth limiting mechanisms, e.g., to escape the feedback controls that normally stop cellular growth and reproduction after a given number of such cells have developed. Cell division and transcription are highly coordinated processes that play important roles in this feedback control. See, e.g., Beeson, et al. (eds. 1979) Textbook of Medicine, 15th ed., W.B. Saunders Co., Philadelphia, PA.; DeVita, et al. (eds. 1997) Cancer: Principles and Practice of Oncology, 5th ed., Lippincott, Philadelphia, PA; Neal and Hoskin (1997) Clinical Oncology: Basic Principles and Practice Oxford University Press, NY; Kastan (1997) Checkpoint Controls and Cancer CSH Press, NY; and Thomas (ed. 1996) Apoptosis and Cell Cycle Control in Cancer: Basic Mechanisms and Implications for Treating Malignant Disease BIOS Scientific, Oxford.

Molecules which function to regulate cell division play important roles in the controlled growth of various types of cells. Aberrations in these controls can lead to various disease states, e.g., oncogenesis, improper wound healing, developmental abnormalities, and metabolic problems.

The cell cycle can be divided into four phases: the presynthetic phases (G_0 and G_1); the phase of DNA synthesis (S); and the postsynthetic phase (G_2). See, e.g., Guyton (ed. 1976) Textbook of Medical Physiology, 5th ed., W.B. Saunders Co., Philadelphia, PA.; Alberts, et al. (eds. 1994) Molecular Biology of the Cell, 3rd ed., Garland Publishing, New York, NY; and Darnell, et al. (eds. 1990) Molecular Cell Biology, 2nd ed., W.H. Freeman, New York, NY. Effective chemotherapeutic agents are often those which target diseased cells in the S phase, e.g., choriocarcinoma, acute lymphocytic leukemia, lyphocytic lymphosarcoma, Burkitt's lymphoma, Hodgkin's disease, testicular neoplasms, Wilm's tumor, and Ewing's sarcoma. Unfortunately, oncogenic cells not actively dividing are less sensitive to these agents.

The lack of knowledge regarding the control of the cell cycle has hampered the ability of medical science to specifically regulate cell division or immune responses. The present invention

provides compositions which will be important in the control of cell division and transcription.

SUMMARY OF THE INVENTION

The present invention is based, in part, upon the characterization of the genes and products relating to the DC-PGT, HDTEA84, HSLJD37R, RANKL, HCC5 chemokine, Dub11, Dub12, MD-1, MD-2, and cyclin E2. It provides nucleic acids, polypeptides, antibodies, and methods for making and using such compositions.

In the DC-PGT embodiments, the invention provides an isolated or recombinant antigenic polypeptide comprising: a plurality of distinct segments, wherein each segment has identity to at least 12 contiguous amino acids from the mature SEQ ID NO: 2; or at least 17 contiguous amino acids from the mature SEQ ID NO: 2. In certain embodiments, the plurality of segments includes one of at least 19 contiguous amino acids; or two of at least 15 contiguous amino acids. Other polypeptides include those wherein the polypeptide: comprises the mature SEQ ID NO: 2; binds with specificity to a polyclonal antibody which specifically binds to SEQ ID NO: 2; or the polypeptide: is a natural allelic variant of SEQ ID NO: 2; is at least 30 amino acids in length; exhibits at least two non-overlapping epitopes specific for SEQ ID NO: 2; is a synthetic polypeptide; is attached to a solid substrate; or is a 5-fold or less conservative substitution from SEQ ID NO: 2. Fusion polypeptides are also provided, e.g., comprising first and second portions, the first portion comprising a sequence as described and the second portion comprising a detectable marker. Pharmaceutical compositions are made available, e.g., comprising a sterile polypeptide, as described, in a pharmaceutically acceptable carrier.

Polynucleotide embodiments include an isolated or recombinant polynucleotide encoding a described polypeptide. Preferred forms will be such a polynucleotide which: comprises the mature polypeptide coding portion of SEQ ID NO: 1; or encodes the mature SEQ ID NO: 2. Preferred embodiments include wherein the polynucleotide is: a PCR product; a hybridization probe; a

mutagenesis primer; or made by chemical synthesis. Alternatively, the polynucleotide is: detectably labeled; a deoxyribonucleic acid; or double stranded. Also provided is an expression vector: comprising the described polynucleotide, including wherein the polypeptide specifically binds polyclonal antibodies generated against an immunogen of mature SEQ ID NO: 2; which selectively hybridizes under stringent hybridization conditions to a target polynucleotide sequence having at least 60 contiguous nucleotides from SEQ ID NO: 1; encodes a polypeptide having at least 50 contiguous amino acid residues from mature SEQ ID NO: 2; or is suitable for transfection into a prokaryote or eukaryote host cell. Preferably, the host cell is: a mammalian cell; a bacterial cell; an insect cell; a prokaryote; a eukaryote; or a COS cell. A method is provided, e.g., of making a polypeptide comprising expressing the vector in the host cell.

Other polynucleotides include an isolated or recombinant polynucleotide which hybridizes to the coding portion of SEQ ID NO: 1 under stringent hybridization and wash conditions of at least 50° C, a salt concentration of less than 400 mM, and 50% formamide. Such a nucleic acid may be an expression vector, which may hybridize to the coding portion of SEQ ID NO: 1 under stringent hybridization and wash conditions of at least 60° C, a salt concentration of less than 200 mM, and 50% formamide. Preferably, the vector encodes a polypeptide which specifically binds an antibody generated against a mature SEQ ID NO: 2. Another embodiment will be such a polynucleotide which hybridizes to SEQ ID NO: 1, wherein the polynucleotide is: a PCR product; a hybridization probe; a mutagenesis primer; or made by chemical synthesis.

Methods are provided, e.g., of modulating the physiology or development of a cell, comprising contacting the cell with an agonist or antagonist of a described polypeptide; of detecting the presence of a complementary polynucleotide in a sample, comprising contacting a described polynucleotide that selectively hybridizes with the complementary polynucleotide in the sample to form a detectable duplex; thereby indicating the presence of the polynucleotide in the sample; or for identifying a compound that

binds to a described polypeptide, comprising: incubating components comprising the compound and the polypeptide under conditions sufficient to allow the components to interact; and measuring the binding of the compound to the polypeptide.

In TNF receptor-like embodiments, the invention further provides an isolated or recombinant polynucleotide encoding an antigenic polypeptide comprising at least 17 contiguous amino acids from: the mature polypeptide from SEQ ID NO: 6; the mature polypeptide from SEQ ID NO: 8; the mature polypeptide from SEQ ID NO: 10; the mature polypeptide from SEQ ID NO: 12; the mature polypeptide from SEQ ID NO: 17; the mature polypeptide from SEQ ID NO: 19; the mature polypeptide from SEQ ID NO: 21; or the mature polypeptide from SEQ ID NO: 23. In preferred embodiments, such polynucleotide will encode all of the polypeptide of: signal processed SEQ ID NO: 6; signal processed SEQ ID NO: 8; signal processed SEQ ID NO: 10; signal processed SEQ ID NO: 12; signal processed SEQ ID NO: 17; SEQ ID NO: 19; SEQ ID NO: 21; or SEQ ID NO: 23. Other embodiments include such a polynucleotide, which hybridizes at 55° C, less than 500 mM salt, and 50% formamide to the: mature protein coding portion of SEQ ID NO: 5; signal processed coding portion of SEQ ID NO: 7; signal processed coding portion of SEQ ID NO: 9; signal processed coding portion of SEQ ID NO: 11; mature protein coding portion of SEQ ID NO: 16; polypeptide coding portion of SEQ ID NO: 18; polypeptide coding portion of SEQ ID NO: 20; or polypeptide coding portion of SEQ ID NO: 22. Other forms include those polynucleotides, comprising at least 35 contiguous nucleotides of: mature protein coding portion of SEQ ID NO: 5; signal processed coding portion of SEQ ID NO: 7; signal processed coding portion of SEQ ID NO: 9; signal processed coding portion of SEQ ID NO: 11; mature protein coding portion of SEQ ID NO: 16; polypeptide coding portion of SEQ ID NO: 18; polypeptide coding portion of SEQ ID NO: 20; or polypeptide coding portion of SEQ ID NO: 22. Various expression vectors are provided comprising such a polynucleotide. The invention also provides a host cell containing the expression vector, including a eukaryotic cell.

Methods are provided, e.g., making an antigenic polypeptide comprising expressing a recombinant polynucleotide; for detecting a polynucleotide, comprising contacting the polynucleotide with a probe that hybridizes, under stringent conditions, to at least 25 contiguous nucleotides of the: mature protein coding portion of SEQ ID NO: 5; signal processed coding portion of SEQ ID NO: 7; signal processed coding portion of SEQ ID NO: 9; signal processed coding portion of SEQ ID NO: 11; mature protein coding portion of SEQ ID NO: 16; polypeptide coding portion of SEQ ID NO: 18; polypeptide coding portion of SEQ ID NO: 20; or polypeptide coding portion of SEQ ID NO: 22; to form a duplex, wherein detection of the duplex indicates the presence of the polynucleotide. Kits are provided, e.g., for the detection of a described polynucleotide, comprising a compartment containing a probe that hybridizes, under stringent hybridization conditions, to at least 17 contiguous nucleotides of a described polynucleotide to form a duplex. Preferably, the probe is detectably labeled.

Binding compounds are provided, including antibodies, comprising an antibody binding site which specifically binds to a polypeptide comprising at least 17 contiguous amino acids from: signal processed SEQ ID NO: 6; signal processed SEQ ID NO: 8; signal processed SEQ ID NO: 10; signal processed SEQ ID NO: 12; signal processed SEQ ID NO: 17; SEQ ID NO: 19;SEQ ID NO: 21; or SEQ ID NO: 23. Preferably, the antibody binding site is: selectively immunoreactive with the: signal processed SEQ ID NO: 6; signal processed SEQ ID NO: 8; signal processed SEQ ID NO: 10; signal processed SEQ ID NO: 12; signal processed SEQ ID NO: 17; SEQ ID NO: 19; SEQ ID NO: 21; or SEQ ID NO: 23; raised against a purified or recombinantly produced human HDTEA84 protein; raised against a purified or recombinantly produced human HSLJD37R protein; or in a monoclonal antibody, Fab, or F(ab)2; or the binding compound is: an antibody molecule; a polyclonal antiserum; detectably labeled; sterile; or in a buffered composition.

Such compositions allow various methods, including using the binding compound, comprising contacting the binding compound with a biological sample comprising an antigen, thereby forming a binding compound:antigen complex. Preferably, the biological

sample is from a human, and the binding compound is an antibody. Such also allow for production of a detection kit comprising the binding compound, and: instructional material for the use of the binding compound for the detection; or a compartment providing segregation of the binding compound.

Polypeptides are also made available, e.g., a substantially pure or isolated antigenic polypeptide, which binds to the described binding composition, and further comprises at least 17 contiguous amino acids from: signal processed SEQ ID NO: 6; signal processed SEQ ID NO: 8; signal processed SEQ ID NO: 10; signal processed SEQ ID NO: 12; signal processed SEQ ID NO: 17; SEQ ID NO: 19; SEQ ID NO: 21; or SEQ ID NO: 23. Preferred polypeptides include those which: comprise at least a fragment of at least 25 contiguous amino acid residues from: a primate HDTEA84 protein; a primate HSLJD37R protein; or a rodent or primate RANKL protein; or are soluble polypeptides; are detectably labeled; are in a sterile composition; are in a buffered composition; bind to an sialic acid residue; are recombinantly produced; or have a naturally occurring polypeptide sequence. In other embodiments, the polypeptide comprises at least 17 contiguous amino acids from the: signal processed SEQ ID NO: 6; signal processed SEQ ID NO: 8; signal processed SEQ ID NO: 12; signal processed SEQ ID NO: 17; SEQ ID NO: 19; SEQ ID NO: 21; or SEQ ID NO: 23.

Methods are provided, including a method of modulating a precursor cell physiology or function comprising a step of contacting the cell with: a binding compound which binds to a described polypeptide; an HDTEA84 polypeptide; an HSLJD37R polypeptide; or a RANKL polypeptide. The method may be one wherein the contacting is in combination with a TNF family ligand, or an antagonist of the TNF family ligand.

In other embodiments, the present invention provides compositions related to other chemokine, Dub, or surface protein genes. Polypeptide embodiments include: a substantially pure or recombinant HCC5 polypeptide exhibiting identity over a length of at least 12 amino acids to SEQ ID NO: 25; an isolated natural sequence HCC5 of mature SEQ ID NO: 25; a fusion protein comprising HCC5 sequence; a substantially pure or recombinant Dub11

polypeptide exhibiting identity over a length of at least about 12 amino acids to SEQ ID NO: 32 or 34; an isolated natural sequence Dub11 of mature SEQ ID NO: 32 or 34; a fusion protein comprising Dub11 sequence; a substantially pure or recombinant Dub12 polypeptide exhibiting identity over a length of at least about 12 amino acids to SEQ ID NO: 36 or 38; an isolated natural sequence Dub12 of mature SEQ ID NO: 36 or 38; a fusion protein comprising Dub12 sequence; a substantially pure or recombinant MD-1 polypeptide exhibiting identity over a length of at least about 12 amino acids to SEQ ID NO: 42; an isolated natural sequence MD-1 of mature SEQ ID NO: 42; a fusion protein comprising primate MD-1 sequence; a substantially pure or recombinant MD-2 polypeptide exhibiting identity over a length of at least about 12 amino acids to SEQ ID NO: 44 or 46; an isolated natural sequence MD-2 of mature SEQ ID NO: 44 or 46; a fusion protein comprising primate MD-2 sequence; a substantially pure or recombinant MD-2 polypeptide exhibiting identity over a length of at least about 12 amino acids to SEQ ID NO: 48 or 49; an isolated natural sequence MD-2 of mature SEQ ID NO: 48; or a fusion protein comprising murine MD-2 sequence. Preferred embodiments include substantially pure or isolated polypeptides which match the sequences over a stretch of at least 17 amino acids; more preferably over a stretch of at least 21 amino acids; over 25, 30, 35, 50, 75 or more. In other preferred embodiments, the HCC5 polypeptide: is from a primate, including a human; comprises at least one polypeptide segment of SEQ ID NO: 25; exhibits a plurality of portions exhibiting the identity; is a natural allelic variant of HCC5; has a length at least about 30 amino acids; exhibits at least two non-overlapping epitopes which are specific for a primate HCC5; exhibits a sequence identity over a length of at least 35 amino acids to a HCC5; is glycosylated; is a synthetic polypeptide; is attached to a solid substrate; is conjugated to another chemical moiety; is a 5-fold or less substitution from natural sequence; or is a deletion or insertion variant from a natural sequence; or the Dub11 polypeptide: is from a primate, including a human; comprises at least one polypeptide segment of SEQ ID NO: 32 or 34; exhibits a plurality of portions exhibiting the identity; is a natural

allelic variant of Dub11; has a length at least about 30 amino acids; exhibits at least two non-overlapping epitopes which are specific for a primate Dub11; exhibits a sequence identity over a length of at least about 35 amino acids to a Dub11; is glycosylated; is a synthetic polypeptide; is attached to a solid substrate; is conjugated to another chemical moiety; is a 5-fold or less substitution from natural sequence; or is a deletion or insertion variant from a natural sequence; or the Dub12 polypeptide: is from a primate, including a human; comprises at least one polypeptide segment of SEQ ID NO: 36 or 38; exhibits a plurality of portions exhibiting the identity; is a natural allelic variant of Dub12; has a length at least about 30 amino acids; exhibits at least two non-overlapping epitopes which are specific for a primate Dub12; exhibits a sequence identity over a length of at least about 35 amino acids to a Dub12; is glycosylated; is a synthetic polypeptide; is attached to a solid substrate; is conjugated to another chemical moiety; is a 5-fold or less substitution from natural sequence; or is a deletion or insertion variant from a natural sequence; or the primate MD-1 polypeptide: is from a human; comprises at least one polypeptide segment of SEQ ID NO: 42; exhibits a plurality of portions exhibiting the identity; is a natural allelic variant of primate MD-1; has a length at least about 30 amino acids; exhibits at least two non-overlapping epitopes which are specific for a primate MD-1; exhibits a sequence identity over a length of at least about 35 amino acids to a primate MD-1; is glycosylated; is a synthetic polypeptide; is attached to a solid substrate; is conjugated to another chemical moiety; is a 5-fold or less substitution from natural sequence; or is a deletion or insertion variant from a natural sequence; or the primate MD-2 polypeptide: is from a human; comprises at least one polypeptide segment of SEQ ID NO: 44 or 46; exhibits a plurality of portions exhibiting the identity; is a natural allelic variant of primate MD-2; has a length at least about 30 amino acids; exhibits at least two non-overlapping epitopes which are specific for a primate MD-2; exhibits a sequence identity over a length of at least about 35 amino acids to a primate MD-2; is glycosylated; is a synthetic

polypeptide; is attached to a solid substrate; is conjugated to another chemical moiety; is a 5-fold or less substitution from natural sequence; or is a deletion or insertion variant from a natural sequence; or the rodent MD-2 polypeptide: is from a mouse; comprises at least one polypeptide segment of SEQ ID NO: 48 or 49; exhibits a plurality of portions exhibiting the identity; is a natural allelic variant of rodent MD-2; has a length at least about 30 amino acids; exhibits at least two non-overlapping epitopes which are specific for a rodent MD-2; exhibits a sequence identity over a length of at least about 35 amino acids to a rodent MD-2; is glycosylated; is a synthetic polypeptide; is attached to a solid substrate; is conjugated to another chemical moiety; is a 5-fold or less substitution from natural sequence; or is a deletion or insertion variant from a natural sequence. Sterile compositions comprising such polypeptides are also provided, along with those comprising: the HCC5 polypeptide and: a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration; another chemokine, including one selected from the group of HCC1, HCC2, HCC3, and HCC4; or an antibody antagonist for a chemokine, including one selected from the group of HCC1, HCC2, HCC3, and HCC4; the Dub11 polypeptide and a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration; the Dub12 polypeptide and a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration; the MD-1 polypeptide and a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration; the MD-2 polypeptide and a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration.

Fusion proteins are provided, e.g., comprising: mature protein sequence of SEQ ID NO: 25; mature protein sequence of SEQ

ID NO: 32, SEQ ID NO: 34, SEQ ID NO: 36 or SEQ ID NO: 38; mature protein sequence of SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, or SEQ ID NO: 49; a detection or purification tag, including a FLAG, His6, or Ig sequence; or sequence of another chemokine protein with the chemokine polypeptide Kits are provided, e.g., comprising a described polypeptide and: a compartment comprising the polypeptide; and/or instructions for use or disposal of reagents in the kit.

Binding compounds, including antibodies, are provided, e.g., comprising an antigen binding portion from an antibody, which specifically binds to a natural: HCC5 polypeptide, wherein the antibody: is raised against a peptide sequence of a mature HCC5 polypeptide sequence of SEQ ID NO: 25; is raised against a mature HCC5; is raised to a purified HCC5; is immunoselected; is a polyclonal antibody; binds to a denatured HCC5; or exhibits a Kd to HCC5 antigen of at least 30 μM; or Dub11 polypeptide, wherein the antibody: is raised against a peptide sequence of a mature Dub11 polypeptide sequence of SEQ ID NO: 32 or SEQ ID NO: 34; is raised against a mature Dub11; is raised to a purified Dub11; is immunoselected; is a polyclonal antibody; binds to a denatured Dub11; or exhibits a Kd to Dub11 antigen of at least 30 μM; or Dub12 polypeptide, wherein the antibody: is raised against a peptide sequence of a mature Dub12 polypeptide sequence of SEQ ID NO: 36 or SEQ ID NO:38; is raised against a mature Dub12; is raised to a purified Dub12; is immunoselected; is a polyclonal antibody; binds to a denatured Dub12; or exhibits a Kd to Dub12 antigen of at least 30 μM; or a primate MD-1 polypeptide, wherein the antibody: is raised against a peptide sequence of a mature polypeptide sequence of SEQ ID NO: 42; is raised against a mature MD-1; is raised to a purified MD-1; is immunoselected; is a polyclonal antibody; binds to a denatured MD-1; or exhibits a Kd to MD-1 antigen of at least 30 μM; or a primate MD-2 polypeptide, wherein the antibody: is raised against a peptide sequence of a mature MD-2 polypeptide sequence of SEQ ID NO: 44, or SEQ ID NO: 46; is raised against a mature MD-2; is raised to a purified MD-2; is immunoselected; is a polyclonal antibody; binds to a denatured

MD-2; or exhibits a Kd to MD-2 antigen of at least 30 μM; or a rodent MD-2 polypeptide, wherein the antibody: is raised against a peptide sequence of a mature MD-2 polypeptide sequence of SEQ ID NO: 48, or SEQ ID NO: 49; is raised against a mature rodent MD-2; is raised to a purified rodent MD-2; is immunoselected; is a polyclonal antibody; binds to a denatured rodent MD-2; or exhibits a Kd to antigen of at least 30 μM. In certain embodiments, the binding composition will be one wherein: the polypeptide is from a primate or rodent; the binding compound is an Fv, Fab, or Fab2 fragment; the binding compound is conjugated to another chemical moiety; is attached to a solid substrate, including a bead or plastic membrane; is in a sterile composition; or is detectably labeled, including a radioactive or fluorescent label.

Kits are provided comprising the binding compound, and: a compartment comprising the binding compound; a compartment comprising purified antigen; and/or instructions for use or disposal of reagents in the kit. Methods are provided for producing an antigen:antibody complex, comprising contacting an antibody and: a primate HCC5 polypeptide; a primate Dub11 polypeptide; a primate Dub12 polypeptide; a primate MD-1 polypeptide; a primate MD-2 polypeptide; or a rodent MD-2 polypeptide; thereby allowing the complex to form. Other compositions are provided, e.g., the binding compound and: a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration; or an antibody antagonist for another chemokine, including one selected from the group of HCC1, HCC2, HCC3, and HCC4.

Nucleic acid embodiments include, e.g., an isolated or recombinant nucleic acid encoding a polypeptide or fusion protein described, wherein: the HCC5: polypeptide is from a primate, including a human; or nucleic acid: encodes an antigenic HCC5 peptide sequence of SEQ ID NO: 25 encodes a plurality of antigenic HCC5 peptide sequences of SEQ ID NO: 25; exhibits identity over at least 25 nucleotides to a natural cDNA encoding the HCC5 segment; is a hybridization probe for a gene encoding the HCC5 polypeptide;

or further encodes another chemokine, including one selected from the group of HCC1, HCC2, HCC3, and HCC4; or the Dub11: polypeptide is from a primate, including a human; or nucleic acid: encodes a Dub11 antigenic peptide sequence of SEQ ID NO: 32; or SEQ ID NO: 34; encodes a plurality of antigenic peptide sequences of SEQ ID NO: 32 or SEQ ID NO: 34; exhibits identity over at least 25 nucleotides to a natural cDNA encoding the Dub11 segment; or is a hybridization probe for a gene encoding the Dub11 polypeptide; the Dub12: polypeptide is from a primate, including a human; or nucleic acid: encodes an antigenic Dub12 peptide sequence of SEQ ID NO: 36 or SEQ ID NO: 38; encodes a plurality of antigenic peptide sequences of SEQ ID NO: 36 or SEQ ID NO: 38; exhibits identity over at least 25 nucleotides to a natural cDNA encoding the DUB12 segment; is a hybridization probe for a gene encoding the Dub12 polypeptide; or the primate MD-1: polypeptide is from a primate, including a human; or nucleic acid: encodes an antigenic MD-1 peptide sequence of SEQ ID NO: 42; encodes a plurality of antigenic peptide sequences of SEQ ID NO: 42; exhibits identity over at least 25 nucleotides to a natural cDNA encoding the MD-1 segment; is a hybridization probe for a gene encoding the Dub11 polypeptide; or the primate MD-2: polypeptide is from a human; or nucleic acid: encodes an antigenic MD-2 peptide sequence of SEQ ID NO: 44, or SEQ ID NO: 46; encodes a plurality of antigenic peptide sequences of SEQ ID NO: 44, or SEQ ID NO: 46; exhibits identity over at least 25 nucleotides to a natural cDNA encoding the segment; is a hybridization probe for a gene encoding the primate MD-2 polypeptide; or the rodent MD-2: polypeptide is from a mouse; or nucleic acid: encodes an antigenic MD-2 peptide sequence of SEQ ID NO: 48, or SEQ ID NO: 49; encodes a plurality of antigenic peptide sequences of SEQ ID NO: 48, or SEQ ID NO: 49; exhibits identity over at least 25 nucleotides to a natural cDNA encoding the MD-2 segment; or is a hybridization probe for a gene encoding the rodent MD-2 polypeptide. Other nucleic acid embodiments include the described, which: is an expression vector; further comprises an origin of replication; is from a natural source; comprises a detectable label; comprises synthetic nucleotide sequence is less than 6 kb, preferably less than 3 kb; is from a

primate, including a human; comprises a natural full length coding sequence; or is a PCR primer, PCR product, or mutagenesis primer.

Various cells are provided, including a cell or tissue comprising a described recombinant nucleic acid, including wherein the cell is: a prokaryotic cell; a eukaryotic cell; a bacterial cell; a yeast cell; an insect cell; a mammalian cell; a mouse cell; a primate cell; or a human cell.

Kits are provided, e.g., comprising a described nucleic acid, and: a compartment comprising the nucleic acid; a compartment comprising a nucleic acid encoding another chemokine, including HCC1, HCC2, HCC3, and HCC4; or instructions for use or disposal of reagents in the kit.

Alternative nucleic acids include those which: hybridize under wash conditions of 45° C and less than 2M salt to the polypeptide coding portion of SEQ ID NO: 24; hybridize under wash conditions of 45° C and less than 2M salt to the polypeptide coding portions of SEQ ID NO: 31 or 33; hybridize under wash conditions of 45° C and less than 2M salt to the coding portions of SEQ ID NO: 35 or 37; hybridize under wash conditions of 45° C and less than 2M salt to the coding portion of SEQ ID NO: 41; hybridize under wash conditions of 45° C and less than 2M salt to the coding portion of SEQ ID NO: 43 or 45. or hybridize under wash conditions of 45° C and less than 2M salt to the coding portion of SEQ ID NO: 47. Preferably, the wash conditions are at 55° C and/or 500 mM salt; or at 65° C and/or 150 mM salt.

Additionally, methods are provided, e.g., of modulating physiology or development of a cell or tissue culture cells comprising exposing the cell to an agonist or antagonist of HCC5, primate MD-1, primate MD-2, or rodent MD-2. Others include methods of detecting specific binding to a compound, comprising: contacting the compound to a composition selected from the group of: an antigen binding site which specifically binds to: an HCC5 chemokine; a Dub11; a Dub12; a primate MD-1; a primate MD-2; a rodent MD-2; or an expression vector encoding: an HCC5 chemokine or fragment thereof; a Dub11 or fragment thereof; a Dub12 or fragment thereof; a primate MD-1 or fragment thereof; a primate MD-2 or fragment thereof; or a rodent MD-2 or fragment thereof; a

substantially pure protein which is specifically recognized by the antigen binding site of the described antigen binding sites; a substantially pure HCC5 chemokine or peptide thereof, or a fusion protein comprising a 30 amino acid sequence portion of HCC5 chemokine sequence; a substantially pure Dub11 or peptide thereof, or a fusion protein comprising a 30 amino acid sequence portion of Dub11 sequence; a substantially pure Dub12 or peptide thereof, or a fusion protein comprising a 30 amino acid sequence portion of Dub11 sequence; a substantially pure primate MD-1 or peptide thereof, or a fusion protein comprising a 30 amino acid sequence portion of primate MD-1 sequence; a substantially pure primate MD-2 or peptide thereof, or a fusion protein comprising a 30 amino acid sequence portion of primate MD-2 sequence; a substantially pure rodent MD-2 or peptide thereof, or a fusion protein comprising a 30 amino acid sequence portion of rodent MD-2 sequence; and then detecting binding of the compound to the composition.

Particular polynucleotide embodiments include an isolated or recombinant polynucleotide which: encodes at least 17 contiguous amino acid residues of SEQ ID NO: 54; encodes at least two distinct segments of at least 10 contiguous amino acid residues of SEQ ID NO 54; or comprises one or more segments at least 21 contiguous nucleotides of SEQ ID NO: 53. Such polynucleotides allow methods of making: a polypeptide comprising expressing a described expression vector, thereby producing the polypeptide; a duplex nucleic acid comprising contacting a polynucleotide with a complementary nucleic acid, thereby resulting in production of the duplex nucleic acid; a synthetic polynucleotide, comprising chemically polymerizing nucleotides to produce the polynucleotide; or a polynucleotide comprising using a PCR method.

Cyclin polypeptide embodiments include an isolated or recombinant antigenic polypeptide comprising at least: one segment comprising at least 17 contiguous amino acids from SEQ ID NO: 54; or at least two distinct segments of at least 11 contiguous amino acids from SEQ ID NO: 54. Such polypeptide may: comprise at least one segment comprising at least 17 contiguous amino acids from SEQ ID NO: 54; and exhibit at least two non-overlapping epitopes which

are selective for primate protein of SEQ ID NO: 54. Other embodiments include those wherein the polypeptide: is a 5-fold or less substitution from a natural sequence; is a deletion or insertion variant from a natural sequence; or comprises at least two distinct segments of at least 11 contiguous amino acids from SEQ ID NO: 54. Preferably the polypeptide is antigenic, and will typically comprise at least one sequence from (SEQ ID NO: 54) KESRYVHD (residues 120-127), DKHFEVLH (residues 127-134), HSDLEPQM (residues 134-141), QKDINKNM (residues 177-184), YAPKLQEF (residues 203-210), SEEDILRM (residues 219-226), LRMELIIL (residues 224-231), ELCPVTII (residues 237-244), and LFLQVDAL (residues 249-256); and/or the segments of at least 11 contiguous amino acids comprise one the segment with at least 14 contiguous amino acids from SEQ ID NO: 54. Such polypeptides may further exhibit at least two non-overlapping epitopes which are selective for primate protein of SEQ ID NO: 54; and/or may: comprise a mature sequence of SEQ ID NO: 2; bind with selectivity to an antibody generated against an immunogen of SEQ ID NO: 54; comprise a plurality of polypeptide segments of 17 contiguous amino acids of SEQ ID NO: 54; or be a natural allelic variant of SEQ ID NO: 54. The polypeptide may: be in a sterile composition; have a length at least 30 amino acids; be not glycosylated; be denatured; be a synthetic polypeptide; be attached to a solid substrate; or be a fusion protein with a detection or purification tag, including a FLAG, His6, or Ig sequence. Other embodiments include those wherein the polypeptide: is a 5-fold or less substitution from a natural sequence; or is a deletion or insertion variant from a natural sequence.

Various kits are provided, e.g., which comprise such polypeptides and instructions for the use or disposal of the polypeptide or other reagents of the kit.

Methods are provided, e.g., to label the polypeptide, comprising labeling the polypeptide with a radioactive label; to separate the polypeptide from another polypeptide in a mixture, comprising running the mixture on a chromatography matrix, thereby separating the polypeptides; to identify a compound that binds selectively to the polypeptide, comprising incubating the compound

with the polypeptide under appropriate conditions; thereby causing the component to bind to the polypeptide; to conjugate the polypeptide to a matrix, comprising derivatizing the polypeptide with a reactive reagent, and conjugating the polypeptide to the matrix; or inducing an antibody response to the polypeptide, comprising introducing the polypeptide as an antigen to an immune system, thereby inducing the response.

Binding compounds are provided, e.g., antibodies, comprising an antigen binding portion from an antibody which binds with selectivity to described polypeptides. Methods are made available for evaluating the selectivity of binding of a compound to cyclin E2, comprising contacting the compound to a recombinant cyclin E2 polypeptide and at least one other cyclin; and comparing binding of the compound to the cyclins.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

All references cited herein are incorporated herein by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

I. General

It is to be understood that this invention is not limited to the particular compositions, methods, and techniques described herein, as such compositions, methods, and techniques may vary. It is to be understood that the terminology used herein is for the purpose of describing particular embodiments, and is not intended to limit the scope of the present invention which is to be limited by the appended claims.

As used herein, including the appended claims, singular forms of words such as "a," "an," and "the" include their corresponding plural referents unless the context clearly dictates otherwise. Thus, e.g., reference to "a polynucleotide" includes one or more different polynucleotides, reference to "a composition" includes one or more of such compositions, and reference to "a method" includes reference to equivalent steps and methods known to a person of ordinary skill in the art, and so forth.

Unless otherwise defined, technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references discussed above are provided for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the invention is not entitled to antedate any such disclosure by virtue of its prior invention.

The present invention also provides amino acid sequences and DNA sequences encoding various mammalian proteins, e.g., which are polypeptides produced by selected cells. Among these proteins are

those which: mediate uptake of substrates, e.g., prostaglandin-like molecules, modulate or mediate, e.g., induce or prevent trafficking, proliferation, or differentiation of, interacting cells, or are intracellular proteins which are important in various cellular processes, e.g., deubiquitination of proteins or cell cycle regulation.

The Prostaglandin-like Transporter (PGT) of the present invention is expressed particularly in antigen presenting cells of the immune system, e.g., dendritic cells. As such, the transporter is designated a dendritic cell prostaglandin-like transporter (DC-PGT). Consequently, the DC-PGT of the present invention offers the means to establish fundamental understanding on the role of PG influence on immune function.

The present invention provides DNA sequence encoding a mammalian protein that exhibits structural features characteristic of functionally significant proteins, particularly which serve as organic anion transporters. This family of organic anion transporters includes: the prostaglandin transporters of man (Lu, et al. (1996) J. Clin. Invest. 98:1142-1149) and rat; organic anion transporters in man and rat; brain digoxyin transporters and Matrin F/G of rat (Kanai, et al. (1995) Science 268:866-869).

Transporters of this family typically are 12 transmembrane proteins of approximately 650 amino acids in length. Characteristic of this group of proteins is a cysteine rich region located in one of the extracellular loops, which resembles a zinc finger motif. It is not entirely certain whether these polypeptides mediate primarily the influx or efflux of prostaglandins and organic anions, and they may, under different circumstances produce influx or efflux depending, e.g., on the intracellular concentration of the organic anions concerned.

The DC PGT protein of the present invention is closest in homology to the prostaglandin transporters and it is probable that a prostaglandin is the major anion transported. The human gene embodiment described herein, isolated as designate DC-PGT or clone 240, contains an open reading frame encoding a presumptive protein of about 709 amino acids. This protein exhibits intracellular, transmembrane, and extracellular protein segments, revealing novel

aspects of organic anion transport that may be relevant during mammalian development, e.g., development of dendritic cells of the immune system.

The introduction of evolutionary information in the form of sequence homologs simplifies the structural analysis considerably for related molecules which share a common structural framework in spite of considerable sequence divergence, see, e.g., Chothia and Lesk (1986) EMBO J. 5:823-826. This concept can be effectively extended to the strong prediction of TM regions across an aligned protein family, whereas any single sequence may provide an uncertain topology. See Persson and Argos (1994) J. Mol. Biol. 237:182-192; and Rost, et al. (1995) Protein Sci. 4:521-533. For the DC PGT, a number of sequence homologs were first assembled by comparative matching to protein and translated nucleotide databases (Altschul, et al. (1994) Nature Genet. 6:119-129; Koonin, et al. (1994) EMBO J. 13:493-503). These relatives of DC-PGT include a ubiquitously expressed PGT from primate, e.g., human (GenBank: locus HSU70867, accession U70867), and a PGT from rodent, e.g., rat (prostaglandin transporter - rat, GenBank Acc. No. 1083766; Kanai, et al. (1995) Science 268:866-869). These sequences were subjected to parallel analyses by a suite of computer programs that have greatly improved on the initial Kyte and Doolittle (1982) hydropathic profile as a means of predicting the topology of integral membrane proteins. Four algorithms (ALOM, MTOP, MEMSAT and TopPredII) (Klein, et al. (1985) Biochim. Biophys. Acta 815:468-476; Hartmann, et al. (1989) Proc. Nat'l Acad. Sci. USA 86:5786-5790; Jones, et al. (1994) Biochem. 33:3038-3049; and Claros and von Heijne (1994) Comp. Applic. Biosci. 10:685-686) were used to individually predict TM extensions and orientations; these predictions were pooled and mapped onto the multiple sequence alignment produced by ClustalW and MACAW (Thompson, et al. (1994) Nucl. Acids Res. 22:4673-4680; and Schuler, et al. (1991) Proteins 9:180-190). Furthermore, these multiply aligned sequence files were used as input to PHD and TMAP (Rost, et al. (1995) Protein Sci. 4:521-533; Persson and Argos (1994) J. Mol. Biol. 237:182-192) for a familial prediction

of shared TM regions. Structural features that persisted in this two-step analysis are likely to be shared topological traits present in all members of this organic anion transporter family.

HDTEA84, HSLJD37R, and RANKL genes and proteins are also provided, which are related to the TNF signaling pathways. The antigens HDTEA84, HSLJD37R, and RANKL, and fragments, or antagonists will be useful in physiological modulation of cells expressing receptors for, e.g., ligands of the TNF family. Some of these antigens appear to lack a membrane spanning segment, suggesting that they are soluble forms of receptor. This suggests that the soluble proteins can serve as antagonists of the TNF-like ligands. In addition, it is likely that membrane spanning forms exist, which serve as signaling receptors mediating cellular response to the ligands.

The HDTEA84 gene has been detected in cDNA libraries derived form Hodgkin's lymphoma, endothelial cells, keratinocytes, prostrate, and cerebellum. It exhibits significant sequence similarity to the osteoprotegerin ligand receptor reported by Lacey, et al. (1998) Cell 93:165-176. The HDTEA84 will likely modulate proliferation or development by antagonizing its respective ligand. Membrane associated forms should exist, likely alternatively spliced transcription products.

The HSLJD37R exhibits like similarity to receptors for TNF. While the first embodiment is an incomplete sequence, the available portion currently lacks an identified transmembrane segment. Additional efforts provide a full length sequence, and an alternative splice variant.

The rodent 427152#4 Rank-like (RANKL) was detected in a rodent cDNA library panel probed with Mouse 427152#4 (204 bp). Positive signals were detected in CH12 (B cell line); rag-1 thymus; rag-1 heart; rag-1 brain (best signal); rag-1 testes; rag-1 liver; normal lung; rag-1 lung; asthmatic lung; tolerized and challenged lung; Nippo-infected lung; Nippo IL-4 K.O. lung; Nippo anti-IL-5 treated lung; influenza lung; guinea pig allergic lung; w.t. stomach; and w.t. colon on a 3 day exposure at -80° C with an intensifier screen. On a 2 week exposure at -80° C with screen, signals were also detected in the following libraries: Mel14+

naive; Mel14+ Th1; Mel14+ Th2; Th1 3 week Bl/6; large B cell; bEnd3 + TNFα + IL-10, guinea pig normal lung; and Rag Hh- colon.

The primate, e.g., human, Rank-like (RANKL) homologs of rodent 427152#4 were detected in a human cDNA library panel probed with mouse 427152#4 (204 bp). Signals were detected in monkey asthma lung 4 h (1.6-2.0 kb) and adult placenta (2.5-3.0 kb) on a 3 day exposure at -80° C with screen. On a 2 week exposure at -80° C with screen, signals were also detected in the following libraries: CD1a+ 95% DC activated CHA (kidney epithelial carcinoma cell line); monkey lung normal; psoriasis skin; fetal lung; fetal ovary; fetal testes; and fetal spleen.

Each of these proteins will also be useful as antigens, e.g., immunogens, for raising antibodies to various epitopes on the protein, linear and/or conformational epitopes. The molecules may be useful in defining various cell subsets, either by the molecules produced by, or by expression of membrane forms of the receptors. Such cells should be responsive to the respective ligands. Soluble forms of the receptors should serve as antagonists of the ligand, binding to the ligand and preventing interaction with membrane forms, which would mediate signaling.

Both genes express proteins which exhibit structural motifs characteristic of a member of the TNF receptor family. SEQ ID NO: 5 and SEQ ID NO: 6, respectively, provide the nucleic acid and predicted amino acid sequences for primate, e.g., human, HDTEA84. SEQ ID NO: 7 and SEQ ID NO: 8, respectively, provide the nucleic acid and predicted amino acid sequences for primate, e.g., human, HSLJD37R.

Interesting features of the HDTEA84 include: signal sequence from about 1-11; TNF receptor Cys rich domains I (about 32-72), II (about 73-113), III (about 114-150), and IV (about 151-193); and unique region from about 194-300. Features for the HSLJD37R (SEQ ID NO: 10 form), partly based on alignment with HDTEA84: signal sequence from about 1-41; TNF receptor Cys rich domains I (about 42-90), II (about 91-131), III (about 132-168), and IV (about 169-211); transmembrane segment from about 354-370. Similar alignment of the other variants will identify similar features. Segments including combinations or excluding such segments may be desired.

The structural homology of HDTEA84, HSLJD37R, and RANKL to members of the TNF receptor family suggests related function of these molecules. See, e.g., Lacey, et al. (1998) Cell 93:165-176. The sequences, however, mostly lack a transmembrane segment, suggesting that the proteins are soluble receptor forms. They may well also have membrane bound forms resulting, e.g., from alternatively spliced transcript variants. The soluble forms are likely to be antagonists of the ligand, e.g., blocking the binding of ligand to a membrane bound form of signaling receptor. Thus, these molecules may be useful in the treatment of abnormal immune or developmental disorders.

The natural antigens should be capable of modulating various biochemical responses which lead to biological or physiological responses in target cells. The embodiments characterized herein are from primate, e.g., human, but other species variants almost surely exist, e.g., rodents, etc. See below. The descriptions below are directed, for exemplary purposes, to primate HDTEA84, HSLJD37R, or RANKL, but are likewise applicable to related embodiments from other species.

The HDTEA84, HSLJD37R, and RANKL clones were assembled through the careful analysis of ESTs present in various databases, e.g., Merck-WashU public database. These genes exhibit structural motifs characteristic of a member of the TNF receptor family. Compare, e.g., with the TNF receptor, NGF-receptor, and FAS receptor. Table 3 discloses the nucleic acid and predicted amino acid sequences for primate, e.g., human, HDTEA84. The ESTs were identified from several different libraries.

SEQ ID NO: 7 AND SEQ ID NO: 8, respectively, disclose partial nucleic acid and predicted amino acid sequences for primate, e.g., human, HSLJD37R. The ESTs were identified from several different libraries derived from: smooth muscle, pancreas tumor, adipocytes, HUVEC cells, adult pulmonary, endothelial cells, prostate cell line PC3, microvascular endothelial cells, fetal heart, and dendritic cells. Other sequences were detected in libraries from: multiple sclerosis lesions, breast, kidney, and germinal center B cells.

SEQ ID NO: 16, SEQ ID NO: 18, SEQ ID NO: 20 and SEQ ID NO: 22 provide the sequences of various mammalian genes designated RANKL.

Interesting features of the rodent RANKL include: signal sequence from about 1-29; TNF receptor Cys rich domain I (about 33-74), II (about 75-114), and III (about 115-135). Interesting features of the primate RANKL include: TNF receptor Cys rich domain I (about 1-43), II (about 44-83), and III (about 84-104); transmembrane segment from about 139-155. Alignment with other TNF receptors will identify additional interesting corresponding features. Segments with boundaries at these positions may be especially interesting.

Hybridization signals with RANKL were detected with rodent, e.g., mouse sequence, in CH12 (B cell line), rag-1 thymus, rag-1 heart, rag-1 brain (strongest signal), rag-1 testes, rag-1 liver, normal lung, rag-1 lung, asthmatic lung, tolerized and challenged lung, Nippo-infected lung, Nippo IL-4 K.O. lung, Nippo anti-IL-5 lung, influenza lung, guinea pig allergic lung, w.t. stomach, and w.t. colon on a 3 day exposure at -80° C with a screen. On a 2 week exposure at -80° C with screen, signals were also detected in the following libraries: Mel 14+ naive, Mel14+ Th1, Mel14+ Th2, Th1 3 week Bl/6, large B cell, bEnd3 + TNFα + IL-10, guinea pig normal lung, and Rag Hh- colon. Probes of human libraries with rodent sequence provided: detectable signals in Monkey asthma lung 4 h (1.6-2.0 kb) and adult placenta (2.5-3.0 kb) on a 3 day exposure at -80° C with screen. On a 2 week exposure at -80° C with screen, signals were also detected in the following libraries: CD1a+ 95% DC activated, CHA (kidney epithelial carcinoma cell line), monkey lung normal, psoriasis skin, fetal lung, fetal ovary, fetal testes, and fetal spleen.

In another embodiment, the invention provides a chemokine. For a review of the chemokine family, see, e.g., Lodi, et al. (1994) Science 263:1762-1767; Gronenborn and Clore (1991) Protein Engineering 4:263-269; Miller and Kranger (1992) Proc. Nat'l Acad. Sci. USA 89:2950-2954; Matsushima and Oppenheim (1989) Cytokine 1:2-13; Stoeckle and Baker (1990) New Biol. 2:313-323; Oppenheim, et al. (1991) Ann. Rev. Immunol. 9:617-648; Schall (1991) Cytokine

3:165-183; and Thomson (ed. 1994) The Cytokine Handbook 2d ed. Academic Press, NY.

The new chemokine described herein is designated HCC5 which is a CC chemokine. See SEQ ID NO: 24 and SEQ ID NO: 25. The descriptions are directed, for exemplary purposes, to the human HCC5 natural allele described, but are likewise applicable to allelic and/or polymorphic variants, e.g., from other individuals, as well as splicing variants, e.g., natural forms. Based on sequence analysis of the chemokine protein sequences described below, it is apparent that HCC5 belongs to the CC chemokine family. See, e.g., stem cell mobilizing chemokine (CKbeta-1) from Kreider, et al. (1997) Patent WO 9715594 (SEQ ID NO: 26) and GenBank Accession number 97P-W17659; macrophage inflammatory protein-1-gamma (MIP-1) from Adams, et al. (1995) Patent WO 9517092 (SEQ ID NO: 27) and GenBank Accession number 95P-R76128; human MIP-4, a chemoattractant for leukocytes from Adams, et al. (1997) Patent WO 9634891 (SEQ ID NO: 28) and GenBank Accession number 96P-W07203; pituitary expressed chemokine (PGEC) from Bandman, et al., Patent WO 9616979 (SEQ ID NO: 29) and GenBank Accession number 96P-R95691; and human chemokine HCC-1 from Forsmann, et al. (1998) Patent WO 9741230 (SEQ ID NO: 30) and GenBank Accession number 97P-W38171.

The HCC5 chemokine was discovered through searches and careful analysis of database sequences. The HCC5 sequence was discovered in a cDNA library from pooled bulk breast tumor tissue. Absence of overlapping sequences from other sources suggests extremely specific tissue expression, or highly regulated expression. Amino acid homology analysis suggests that the HCC5 gene encodes a member of a group of related family of chemokines. The primate, e.g., human, HCC5 chemokine is most closely related in sequence to the chemokines, human chemokine HCC1; human pituitary expressed chemokine (PGEC); human MIP-4 (a chemoattractant for leukocytes); human macrophage inflammatory protein-1-gamma (MIP-1γ); and human stem cell mobilizing chemokine (CKbeta-1).

The HCC5 chemokine is seemingly specifically expressed, since its sequence has not appeared from many sources. The structural

similarity to other chemokines suggests that signals important in inflammation, cell differentiation, and development are mediated by it.

It is possible that the HCC5 may actually be an antagonist of one, some, or all, of many related chemokines. In such case, combination compositions may be desired. For example, a combined group of functional agonists and antagonists for specific receptors may be called for, e.g., a combination of chemokines and antibody antagonists of others. In addition, HCC5 may be useful to block HIV or HTLV infection, which viruses may use the respective receptors for infection.

The HCC5 chemokine exhibits limited similarity to portions of known chemokines. See, e.g., Matsushima and Oppenheim (1989) Cytokine 1:2-13; Oppenheim, et al. (1991) Ann. Rev. Immunol. 9:617-648; Schall (1991) Cytokine 3:165-183; and Gronenborn and Clore (1991) Protein Engineering 4:263-269. Other features of comparison are apparent between the HCC5 chemokine and chemokine families. See, e.g., Lodi, et al. (1994) Science 263:1762-1766. In particular, β-sheet and α-helix residues can be determined using, e.g., RASMOL program, see Sayle and Milner-White (1995) TIBS 20:374-376; or Gronenberg, et al. (1991) Protein Engineering 4:263-269; and other structural features are defined in Lodi, et al. (1994) Science 263:1762-1767. These secondary and tertiary features assist in defining further the C, CC, CXC, and CX3C structural features, along with spacing of appropriate cysteine residues.

Antagonists might be created by N-terminal modification, e.g., either truncation of addition of an N-terminal methionine. Since HCC5 is structurally related to the HCC chemokines, it may well exhibit similar behaviors and functions.

The distribution of the HCC5 chemokines, especially in dendritic cells, or in Th1 T cells, B cells, and macrophages, suggest roles in immune functions, e.g., it will likely attract T cells and monocytes.. Thus, the HCC5 chemokine is likely to recruit these cell types in vivo, thereby enhancing the immune response mediated by these cell types. The expression patterns

appear consistent with a functional importance of the ligands in a TH1/TH2 regulation and/or response, including, e.g., in a cancer therapy. Thus, ligands and homologs are identified as possible immune adjuvants, e.g., for cellular responses, but also as possible adjuvants to modulate soluble antigen responses, e.g., vaccines.

The invention further provides mammalian, e.g., primate, DNA sequences encoding proteins which exhibit structural properties of likely intracellular deubiquitinating protein enzymes. These proteins are designated deubiqutinating 11 (Dub11) and deubiqutinating 12 (Dub12). For a review of the superfamily of deubiquitinating enzymes see, e.g., Hochstrasser (1995) Curr. Opin. Cell Biol. 7:215-223; Wilkinson, et al. (1995) Biochemistry 34:14535-14546; Baker, et al. (1992) J. Biol. Chem. 267:23364-23375; and Papa and Hochstrasser (1993) Nature 366:313-319. However, the deubiquitinating enzymes have also been reported to have additional functions besides deubiquitination. See, e.g., Hochstrasser (1996) Cell 84:813-815; Hicke and Riezman (1996) Cell 84:277-287; and Chen, et al. (1996) Cell 84:853-862.

The descriptions typically are directed, for exemplary purposes, to the human Dub11 and human Dub12 natural alleles described, but are likewise applicable to allelic and/or polymorphic variants, e.g., from other individuals, as well as splicing variants, e.g., natural forms, and species variants from other primates or other species. These genes will allow isolation of other primate genes encoding proteins related to this, further extending the family beyond the specific embodiments described.

The Dub11 or Dub12 proteins (naturally occurring or recombinant), fragments thereof, and antibodies thereto, along with compounds identified as having binding affinity to Dub11 or Dub12, may be useful in the treatment of conditions associated with abnormal physiology or development, such as, e.g., uterine carcinoma associated with p53 dysregulation associated with human papilloma virus or mental retardation of Angelman syndrome (AS) due to disruption of the 5' end of the UBE3A (E6-AP) gene which codes for a disubiquitination protein. Pharmacological intervention which alters the half-lives of cellular proteins

associated with these diseases may have wide therapeutic potential. Specifically, prevention of p53 ubiquitination (and subsequent degradation) in human papilloma virus positive tumors, and perhaps all tumors retaining wild-type p53 but lacking the retinoblastoma gene function, could lead to programmed cell death. Additionally, specific inhibitors of p27 and cyclin B ubiquitination are predicted to be potent antiproliferative agents. Inhibitors of IkappaB ubiquitination should prevent NFkappaB activation and may have utility in a variety of autoimmune and inflammatory conditions. Finally, deubiquitination enzymes may be novel, potential drug targets as they also appear to regulate cell proliferation. These conditions or disease states may be modulated by appropriate therapeutic treatment using the deubiquitination compositions provided herein.

Conversely, methods for blocking the enzymatic activities should have the opposite effects. Small molecule drug screening to block enzymatic activity of the protein can be performed to identify entities which will block the deubiquitination, thereby affecting protein degradation pathways, as appropriate.

The T cell growth factor interleukin-2 (IL-2) regulates lymphocyte proliferation by inducing the expression of growth promoting genes. HTLV-1 transformed cell lines derived from Adult T-cell Leukemia (ATL) can exhibit constitutive activation of the IL-2-induced JAK/STAT pathway. See Migone, et al. (1998) Proc. Nat'l Acad. Sci. USA 95:3845-3850. ATL cell lines were examined for expression of IL-2 induced genes. It was found that the deubiquitinating enzyme Dub2 is constitutively expressed. See Zhu, et al. (1997) J. Biol. Chem. 272:51-57. Moreover, Dub2 expression conferred cytokine-independent proliferation on the interleukin-3-dependent murine Ba/F3 hematopoietic cell line. SCID mice (n = 18) subcutaneously injected with Ba/F3 cells expressing Dub2, (but not a C to S inactive mutant of Dub2) developed tumors with a six week latency. Cells derived from these tumors exhibited constitutive tyrosine phosphorylation of STAT5 and also mimicked the ATL cell lines by exhibiting down-regulation of the protein tyrosine phosphatase SHP-1. These findings strongly indicate that Dub12 is an oncogene that, when

constitutively expressed, can induce cytokine-independent growth in lymphocytes and may be implicated in leukemogenesis. It is likely that Dub2 controls cell growth by regulating the ubiquitin-dependent proteolysis or the ubiquitin-dependent state of a critical intracellular substrate. Functional similarity of the Dub11 and Dub12 would be expected. Thus, the biological role of Dub2 suggests similar important roles for the other Dub family members.

Screening for inhibitors of the DUB enzymes can also be easily accomplished using the known assays for activity. Such assays can be developed into high throughput screening efforts, testing, particularly, compounds known to affect protein turnover, or similar enzymatic sites. Small molecule antagonists of the enzymes, which will be membrane permeable, would be particularly desirable therapeutically.

In the MD embodiments of the present invention, mammalian, e.g., primate, and rodent, e.g., mouse, DNA sequences are provided encoding proteins which exhibit structural properties of ligands for proteins exhibiting a leucine-rich protein motif (LRR) that is important, e.g., in immune function. These proteins are designated herein human MD-1, human MD-2, and murine MD-2. The human MD-1 is a primate homolog of the previously described rodent MD-1, see, e.g., Miyake, et al. (1998) J. Immunol. 161:1348-1353, while human MD-2 and mouse MD-2 are newly discovered MD-1 homolog. For a general review of LRR proteins, see, e.g., Kobe and Deisenhofer (1994) Trends Biochem. Sci. 19:412. For the role of LRR in specific immune defenses, see, e.g., Jones, et al. (1994) Science 266:789; Dixon, et al. (1996) Cell 84:451; and Baker, et al. (1997) Science 276:726.

Similar sequences for proteins in other species should also be available. The descriptions below are directed, for exemplary purposes, to the primate, e.g., human, MD-1 and MD-2, and rodent, e.g., mouse, MD-2 natural alleles described, but are likewise applicable to allelic and/or polymorphic variants, e.g., from other individuals, as well as splicing variants, e.g., natural forms, and species variants.

The MD-1 or MD-2 proteins (naturally occurring or recombinant), fragments thereof, and antibodies thereto, along with compounds identified as having binding affinity to MD-1 or MD-2, should be useful in the treatment of conditions associated with abnormal physiology or development, such as, e.g., the recognition of specific pathogenic molecules and the activation of B cell physiology. As indicated above, MD-1 and MD-2 exhibit structural motifs characteristic of ligands for the RP105 or BAS-1 surface receptors. Thus, soluble forms, antibodies, or small molecule drugs which disrupt intercellular signaling mediated by these receptors, will find use in modulating cellular response. These responses will be important in normal or abnormal clinical situations.

The matching of the MD and RP105 may also be easily tested. Identification of the counter receptor for the MD-2 may include testing both the RP105 and BAS-1 genes, along with other screening methods, as described. The likely counter receptor structure for the MDs are RP105, BAS-1, and related genes. Associated proteins which bind to these, including the DUB proteins, may be identified using these techniques, among others.

Another aspect of the invention provides members of the cyclin proteins. The cyclins and their partner catalytic subunits, the cyclin-dependent kinases (Cdks), play key roles in the regulation of eukaryotic cell cycle events. See, e.g., Draetta (1994) Curr. Opin. Cell Biol. 6:842-846; Sherr (1994) Cell 79:551-555; and Ohtsubo, et al. (1995) Mol. Cell. Biol. 15:2612-2624. Cyclins were first identified in marine invertebrates on the basis of their dramatic cell cycle periodic expression during meiotic and mitotic divisions.

A large family of cyclins, designated cyclins A-H, bind and activate different Cdks which are serine/threonine kinases essential for cell cycle progression. The timing of the expression of the various cyclins is key in determining at which phase of the cell cycle (S, G_0, G_1, or G_2) their associated Cdk is active. D-type cyclins are synthesized early in G_1 and bind and activate CDK4 and CDK6. Cyclin E-Cdk2 and Cyclin A-Cdk2 complexes form later in G_1 as cells prepare to begin DNA synthesis. Cyclin

B-cdc2 is active during G_2 and mitosis. See, e.g., Lees (1995) Curr. Opin. Cell Biol. 7:773-780.

Other Cyclin-Cdk complex associated proteins are critical for modulation of cyclin activity. Proteins that co-immunoprecipitated with cyclin E were visualized by SDS-PAGE. However, viability of the cyclin E "knockout" mouse, suggested the existence of redundancy. Moreover, work in other species also suggested that a homolog might exist in human.

Cdks can also exert control on cell division and proliferation by phosphorylating specific intracellular target proteins. This phosphorylation event can induce the cellular transition from the G_1 to the S phase of the cell cycle. See, e.g., Strahler, et al. (1992) Biochem. Biophys. Res. Comm. 185:197-203; Brattsand, et al. (1994) Eur. J. Biochem. 220:359-368; and Li, et al. (1996) Cell 85:319-329. Regulation of the cell cycle machinery is important in development and control of cellular proliferation. Misregulation may lead to proliferative disorders, e.g., neoplastic conditions and cancer. See, e.g., Sherr (1998) Science 274:1672-1677.

The novel cyclin gene, designated cyclin E2, exhibits about 49% structural identity to the known human cyclin E. See, e.g., Lew, et al. (1991) Cell 66:1197-1206; and NCBI Entrez accession number M74093. The new variant cyclin E2 sequences are provided in SEQ ID NO: 52 and SEQ ID NO: 53. Notable features on the E2 sequence include the cyclin box running from about residue 120-254; and a putative phosphorylation site at thr392. The phosphorylation site is trigger in cyclin E for ubiquitin dependent degradation. See Clurman, et al. (1996) Genes and Development 10:1979-1990. Particularly interesting segments include, e.g., from about 93-100; 98-106; 104-113; 107-121; 120-128; 124-134; 131-137; 172-177; 176-185; 189-193; 196-202; 200-210; 218-223; 228-232; 236-242; 240-245; and 248-252.

The structural homology of these genes to identified families suggests related function of these molecules. For example, PGT homologs should function in transport across cell membranes; TNF receptor family antagonists, or agonists, may act as a co-

stimulatory molecule for regulation of T cell mediated cell activation, and may in fact, cause a shift of T helper cell types, e.g., between Th1 and Th2; chemokines have recognized functional properties; intracellular Dubs have been described and the role in oncogenesis established; membrane associated or soluble forms of signaling proteins such as the MDs are well known; and the role of cyclins in cell cycle regulation are recognized. Alternatively, the ligands or binding structures for the cell surface antigens may serve to regulate cell proliferation or development.

For the TNF ligand molecules, they typically modulate cell proliferation, viability, and differentiation. For example, TNF and FAS can kill cells expressing their respective receptors, including fibroblasts, liver cells, and lymphocytes. Some members of this class of ligands exhibit effects on cellular proliferation of cells expressing their respective receptors, e.g., B cells expressing CD40. These effects on proliferation may also effect subsequent differentiation steps, and may lead, directly or indirectly, to changes in cytokine expression profiles.

The members of the TNF ligand family also exhibit costimulation effects, which may also regulate cellular differentiation or apoptosis. Receptor expressing cells may be protected from activation induced cell death (AICD) or apoptosis. For example, CD40 ligand can have effects on T and B lymphocytes.

The embodiments characterized herein are mostly from human, but additional sequences for proteins in other mammalian species, e.g., primates and rodents, will also be available. See below. In particular, with the polypeptide sequences provided, reverse translation, e.g., using the genetic code, software is available, which will indicate what nucleic acid sequences could encode them. See, e.g., MacVector, Oxford Molecular Group Software. Thus, artificial genes, or redundant oligonucleotides may be selected to isolate natural variants or species counterparts.

II. Purified Protein

Primate, e.g., human, DC-PGT polypeptide sequence is shown in SEQ ID NO: 2; primate, e.g., human, HDTEA84 polypeptide sequence is shown in SEQ ID NO: 6; primate, e.g., human, HSLJD37R

polypeptide sequences are shown in SEQ ID NO: 8, 10, and 12; rodent, e.g., murine, RANKL polypeptide sequence is shown in SEQ ID NO: 17; primate forms of RANKL polypeptide sequence are shown in SEQ ID NO: 19, 21, and 23; primate, e.g., human, HCC5 chemokine polypeptide sequence is shown in SEQ ID NO: 25; primate, e.g., human, Dub11 polypeptide sequences are shown in SEQ ID NO: 32 and 34; primate, e.g., human, Dub12 polypeptide sequences are shown in SEQ ID NO: 36 and 38; primate, e.g., human, MD-1 polypeptide sequence is shown in SEQ ID NO: 42; primate, e.g., human, MD-2 polypeptide sequence is shown in SEQ ID NO: 44 and 46; rodent, e.g., mouse, MD-2 polypeptide sequences are shown in SEQ ID NO: 48 and 49; and primate, e.g., human, cyclin E2 is shown in SEQ ID NO: 54.

These amino acid sequences, provided amino to carboxy, are important in providing sequence information in the antigen allowing for distinguishing the protein from other proteins and exemplifying numerous variants. Moreover, the peptide sequences allow preparation of peptides to generate antibodies to recognize such segments, and nucleotide sequences allow preparation of oligonucleotide probes, both of which are strategies for detection or isolation, e.g., cloning, of genes or cDNAs encoding such sequences.

The purified protein, or proteins will typically comprise a plurality of distinct, e.g., nonoverlapping, segments of the specified length. Typically, the plurality will be at least two, more usually at least three, and preferably 5, 7, or even more. While the length minima are provided, longer lengths, of various sizes, may be appropriate, e.g., one of length 7, and two of length 12. Such peptides are useful for generating antibodies by standard methods, as described herein. Synthetic peptides or purified protein can be presented to an immune system to generate a specific binding composition, e.g., monoclonal or polyclonal antibodies. See, e.g., Coligan (1991) Current Protocols in Immunology Wiley/Greene; and Harlow and Lane (Current ed.) Antibodies: A Laboratory Manual Cold Spring Harbor Press.

For example, the specific binding composition could be used for screening of an expression library made from a cell line which

expresses a clone encoding, e.g., a prostaglandin transporter. The screening can be standard staining of surface expressed protein, or by panning. Screening of intracellular expression can also be performed by various staining or immunofluorescence procedures. The binding compositions could be used to affinity purify or sort out cells expressing the protein. The binding compositions may also be useful in determining qualitative and quantitative expression levels of the proteins in various biological samples, including, e.g., cell types or tissues.

As used herein, the term, e.g., "human DC-PGT", shall encompass, when used in a protein context, a protein having amino acid sequence shown in SEQ ID NO: 2. Significant polypeptide fragments of such a protein should preserve some of the properties, biological or physical, of the full length protein. Other essentially identical or equivalent proteins may be found in other primates or related species. In addition, binding components, e.g., antibodies, typically bind to, e.g., a DC-PGT, with high affinity, e.g., at least about 100 nM, usually better than about 30 nM, preferably better than about 10 nM, and more preferably at better than about 3 nM. Homologous proteins would be found in mammalian species other than human, e.g., primates or rodents. Non-mammalian species should also possess structurally or functionally related genes and proteins, e.g., birds or amphibians. Similar meanings apply in reference to HDTEA84, HSLJD37R, RANKL, HCC5, Dub11, Dub12, MD-1, MD-2, and cyclin E2.

The term polypeptide, as used herein, includes a significant fragment or segment, and encompasses a stretch of amino acid residues of at least about 8 amino acids, generally at least 10 amino acids, more generally at least 12 amino acids, often at least 14 amino acids, more often at least 16 amino acids, typically at least 18 amino acids, more typically at least 20 amino acids, usually at least 22 amino acids, more usually at least 24 amino acids, preferably at least 26 amino acids, more preferably at least 28 amino acids, and, in particularly preferred embodiments, at least about 30 or more amino acids. The segments may have lengths of at least 37, 45, 53, 61, 70, 80, 90, etc., and often will encompass a plurality of such matching sequences. The

specific ends of such a segment will be at any combinations within the protein. In certain embodiments, there will be a plurality of distinct, e.g., nonoverlapping, segments of the specified length. Typically, the plurality will be at least two, more usually at least three, and preferably 5, 7, or even more. While the length minima are provided, longer lengths, of various sizes, may be appropriate, e.g., one of length 7, and two of length 12.

The term "binding composition" refers to molecules that bind with specificity to the respective protein or polypeptide, e.g., DC-PGT, e.g., in a cell adhesion pairing type fashion, or an antibody-antigen interaction. Other compounds include, e.g., proteins, which specifically associate with DC-PGT, including in a natural physiologically relevant protein-protein interaction, either covalent or non-covalent. The molecule may be a polymer, or chemical reagent. A functional analog may be an antigen with structural modifications, or it may be a molecule which has a molecular shape which interacts with the appropriate binding determinants. The compounds may serve as agonists or antagonists of the binding interaction, see, e.g., Goodman, et al. (eds. 1990) Goodman & Gilman's: The Pharmacological Bases of Therapeutics (8th ed.) Pergamon Press.

Substantially pure, in the polypeptide context, typically means that the protein is free from other contaminating proteins, nucleic acids, and other biologicals derived from the original source organism or cell. Purity may be assayed by standard methods, and will ordinarily be at least about 40% pure, more ordinarily at least about 50% pure, generally at least about 60% pure, more generally at least about 70% pure, often at least about 75% pure, more often at least about 80% pure, typically at least about 85% pure, more typically at least about 90% pure, preferably at least about 95% pure, more preferably at least about 98% pure, and in most preferred embodiments, at least 99% pure. The analysis may be weight or molar percentages, evaluated, e.g., by gel staining, spectrophotometry, or terminus labeling. Carriers or excipients will often be subsequently added.

Solubility of a polypeptide or fragment depends upon the environment and the polypeptide. Many parameters affect

polypeptide solubility, including temperature, electrolyte environment, size and molecular characteristics of the polypeptide, and nature of the solvent. Typically, the temperature at which the polypeptide is used ranges from about 4° C to about 65° C. Usually the temperature at use is greater than about 18° C. For diagnostic purposes, the temperature will usually be about room temperature or warmer, but less than the denaturation temperature of components in the assay. For therapeutic purposes, the temperature will usually be body temperature, typically about 37° C for humans and mice, though under certain situations the temperature may be raised or lowered in situ or in vitro.

The size and structure of the polypeptide should generally be in a substantially stable state, and usually not in a denatured state. The polypeptide may be associated with other polypeptides in a quaternary structure, e.g., to confer solubility, or associated with lipids or detergents in a manner which approximates natural lipid bilayer interactions.

The solvent and electrolytes will usually be a biologically compatible buffer, of a type used for preservation of biological activities, and will usually approximate a physiological aqueous solvent. Usually the solvent will have a neutral pH, typically between about 5 and 10, and preferably about 7.5. On some occasions, one or more detergents will be added, typically a mild non-denaturing one, e.g., CHS (cholesteryl hemisuccinate) or CHAPS (3-[3-cholamidopropyl)dimethylammonio]-1-propane sulfonate), or a low enough concentration as to avoid significant disruption of structural or physiological properties of the protein.

Solubility is reflected by sedimentation measured in Svedberg units, which are a measure of the sedimentation velocity of a molecule under particular conditions. The determination of the sedimentation velocity was classically performed in an analytical ultracentrifuge, but is typically now performed in a standard ultracentrifuge. See, Freifelder (1982) Physical Biochemistry (2d ed.), W.H. Freeman; and Cantor and Schimmel (1980) Biophysical Chemistry, parts 1-3, W.H. Freeman & Co., San Francisco; each of which is hereby incorporated herein by reference. As a crude

determination, a sample containing a putatively soluble polypeptide is spun in a standard full sized ultracentrifuge at about 50K rpm for about 10 minutes, and soluble molecules will remain in the supernatant. A soluble particle or polypeptide will typically be less than about 30S, more typically less than about 15S, usually less than about 10S, more usually less than about 6S, and, in particular embodiments, preferably less than about 4S, and more preferably less than about 3S.

The human complimentary DNA and deduced amino acid sequence provided here for DC-PGT contains sequences corresponding to twelve putative transmembrane (TM) segments, based upon a hydropathicity and structural analysis of DC-PGT. A TopPredII (Claros and von Heijne (1994) Comp. Applic. Biosci. 10:685-686) profile of the DC-PGT sequence showing peaks that reach beyond 'putative' or 'certain' baselines. The 12 transmembrane segments correspond to hydrophobic stretches which run approximately from amino acids 47-68 (TM1); 88-107 (TM2); 117-136 (TM3); 188-208 (TM4); 225-244 (TM5); 279-294 (TM6) 367-386 (TM7); 412-431 (TM8); 450-474 (TM9); 561-578 (TM10); 597-616 (TM11); and 651-675 (TM12). Charged amino residues located within the transmembrane domains are: glutamine at amino residues 59, 62, 196, 207, 380, 469, 602, 655, and 675; glutamic acid at residue 95; and arginine at residues 607 and 674. Extracellular loops correspond approximately to amino acid residues 69-87, 137-187, 295-366, 432-449, 579-596, and 617-650. Putative N-glycosylation sites in the exposed, extracellular face of the molecule are located in the second and fifth extracellular loops at Asn-X-Ser/Thr motifs (e.g., 146-148; 176-178; and 538-540). Intracellular portions correspond approximately to amino acid residues 1-46, 108-116, 209-224, 295-366, 432-449, 579-596, and 676-709. These boundaries will often be the boundaries of segments of interest, which be include multiple described segments.

Transporters of this family are typically 12 transmembrane proteins of approximately 650 amino acids in length and include the organic anion transporters in man and rat, prostaglandin transporters of man (Lu, et al. (1996) J. Clin. Invest. 98:1142-1149) and rat; brain digoxyin transporters and Matrin F/G of rat

(Kanai, et al. (1995) Science 268:866-869). Characteristic of this family of organic anion transporter proteins is a cysteine rich region located in one of the extracellular loops, which resembles a zinc finger motif. The DC-PGT cysteine rich region is located in extracellular loop 5 with cysteines approximately at positions 489, 493, 495, 504, 516, 520, 539, 541, 554, and 557.

Other particularly interesting segments of the TNF receptors, Dubs, MDs, and cyclin E are pointed out. These may also be segments of comparison with other proteins or genes.

III. Physical Variants

This invention also encompasses proteins or peptides having substantial amino acid sequence homology with the amino acid sequences of the described proteins. The variants include species and polymorphic variants, e.g., naturally occurring forms.

Amino acid sequence homology, or sequence identity, is determined by optimizing residue matches, if necessary, by introducing gaps as required. See also Needleham, et al. (1970) J. Mol. Biol. 48:443-453; Sankoff, et al. (1983) Chapter One in Time Warps, String Edits, and Macromolecules: The Theory and Practice of Sequence Comparison, Addison-Wesley, Reading, MA; and software packages from IntelliGenetics, Mountain View, CA; and the University of Wisconsin Genetics Computer Group, Madison, WI. Sequence identity changes when considering conservative substitutions as matches. Conservative substitutions typically include substitutions within the following groups: glycine, alanine; valine, isoleucine, leucine; aspartic acid, glutamic acid; asparagine, glutamine; serine, threonine; lysine, arginine; and phenylalanine, tyrosine. Homologous amino acid sequences are typically intended to include natural polymorphic or allelic and interspecies variations in each respective protein sequence. Typical homologous proteins or peptides will have from 25-100% identity (if gaps can be introduced), to 50-100% identity (if conservative substitutions are included) with the amino acid sequence of the HDTEA84. Identity measures will be at least about 35%, generally at least about 40%, often at least about 50%, typically at least about 60%, usually at least about 70%,

preferably at least about 80%, and more preferably at least about 90%.

For sequence comparison, typically one sequence acts as a reference sequence, to which test sequences are compared. When using a sequence comparison algorithm, test and reference sequences are input into a computer, subsequence coordinates are designated, if necessary, and sequence algorithm program parameters are designated. The sequence comparison algorithm then calculates the percent sequence identity for the test sequence(s) relative to the reference sequence, based on the designated program parameters.

Optical alignment of sequences for comparison can be conducted, e.g., by the local homology algorithm of Smith and Waterman (1981) Adv. Appl. Math. 2:482, by the homology alignment algorithm of Needleman and Wunsch (1970) J. Mol. Biol. 48:443, by the search for similarity method of Pearson and Lipman (1988) Proc. Nat'l Acad. Sci. USA 85:2444, by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, WI), or by visual inspection (see generally Ausubel et al., supra).

One example of a useful algorithm is PILEUP. PILEUP creates a multiple sequence alignment from a group of related sequences using progressive, pairwise alignments to show relationship and percent sequence identity. It also plots a tree or dendrogram showing the clustering relationships used to create the alignment. PILEUP uses a simplification of the progressive alignment method of Feng and Doolittle (1987) J. Mol. Evol. 35:351-360. The method used is similar to the method described by Higgins and Sharp (1989) CABIOS 5:151-153. The program can align up to 300 sequences, each of a maximum length of 5,000 nucleotides or amino acids. The multiple alignment procedure begins with the pairwise alignment of the two most similar sequences, producing a cluster of two aligned sequences. This cluster is then aligned to the next most related sequence or cluster of aligned sequences. Two clusters of sequences are aligned by a simple extension of the pairwise alignment of two individual sequences. The final

alignment is achieved by a series of progressive, pairwise alignments. The program is run by designating specific sequences and their amino acid or nucleotide coordinates for regions of sequence comparison and by designating the program parameters. For example, a reference sequence can be compared to other test sequences to determine the percent sequence identity relationship using the following parameters: default gap weight (3.00), default gap length weight (0.10), and weighted end gaps.

Another example of algorithm that is suitable for determining percent sequence identity and sequence similarity is the BLAST algorithm, which is described Altschul, et al. (1990) J. Mol. Biol. 215:403-410. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information (http:www.ncbi.nlm.nih.gov/). This algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query sequence, which either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighborhood word score threshold (Altschul, et al., supra). These initial neighborhood word hits act as seeds for initiating searches to find longer HSPs containing them. The word hits are then extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T, and X determine the sensitivity and speed of the alignment. The BLAST program uses as defaults a wordlength (W) of 11, the BLOSUM62 scoring matrix (see Henikoff and Henikoff (1989) Proc. Nat'l Acad. Sci. USA 89:10915) alignments (B) of 50, expectation (E) of 10, M=5, N=4, and a comparison of both strands.

In addition to calculating percent sequence identity, the BLAST algorithm also performs a statistical analysis of the similarity between two sequences (see, e.g., Karlin and Altschul

(1993) Proc. Nat'l Acad. Sci. USA 90:5873-5787). One measure of similarity provided by the BLAST algorithm is the smallest sum probability (P(N)), which provides an indication of the probability by which a match between two nucleotide or amino acid sequences would occur by chance. For example, a nucleic acid is considered similar to a reference sequence if the smallest sum probability in a comparison of the test nucleic acid to the reference nucleic acid is less than about 0.1, more preferably less than about 0.01, and most preferably less than about 0.001.

A further indication that two nucleic acid sequences of polypeptides are substantially identical is that the polypeptide encoded by the first nucleic acid is immunologically cross reactive with the polypeptide encoded by the second nucleic acid, as described below. Thus, a polypeptide is typically substantially identical to a second polypeptide, for example, where the two peptides differ only by conservative substitutions. Another indication that two nucleic acid sequences are substantially identical is that the two molecules hybridize to each other under stringent conditions, as described below.

The isolated DC-PGT, HDTEA84, HSLJD37R, RANKL, HCC5, Dub, MD-1, MD-2, or cyclin E2 DNAs can be readily modified by nucleotide substitutions, nucleotide deletions, nucleotide insertions, and inversions of nucleotide stretches. These modifications result in novel DNA sequences which encode these antigens, their derivatives, or proteins having similar physiological, immunogenic, antigenic, or other functional activity. These modified sequences can be used to produce mutant antigens or to enhance expression. Enhanced expression may involve gene amplification, increased transcription, increased translation, and other mechanisms. For example, "Mutant HDTEA84" encompasses a polypeptide otherwise falling within the sequence identity definition of the HDTEA84 as set forth above, but having an amino acid sequence which differs from that of HDTEA84 as normally found in nature, whether by way of deletion, substitution, or insertion. This generally includes proteins having significant identity with a protein having sequence of SEQ ID NO: 6, and as sharing various biological activities, e.g., antigenic or immunogenic, with those

sequences, and in preferred embodiments contain most of the full length disclosed sequences. Full length sequences will typically be preferred, though truncated versions, e.g., soluble constructs and intact domains, will also be useful, likewise, genes or proteins found from natural sources are typically most desired. Similar concepts apply to different HDTEA84 proteins, particularly those found in various warm blooded animals, e.g., mammals and birds, or fish. These descriptions are generally meant to encompass all HDTEA84 proteins, not limited to the particular human embodiment specifically discussed. Similar concepts apply to the other polypeptides provided.

DC-PGT, HDTEA84, HSLJD37R, RANKL, HCC5, Dub, MD-1, MD-2, or cyclin E2 mutagenesis can also be conducted by making amino acid insertions or deletions. Although site specific mutation sites are predetermined, mutants need not be site specific. Protein mutagenesis can be conducted by making amino acid insertions or deletions, or combinations may be generated to arrive at a final construct. Insertions include amino- or carboxy- terminal fusions. Random mutagenesis can be conducted at a target codon and the expressed mutants can then be screened for the desired activity. Methods for making substitution mutations at predetermined sites in DNA having a known sequence are well known in the art, e.g., by M13 primer mutagenesis or polymerase chain reaction (PCR) techniques. See, e.g., Sambrook, et al. (1989); Ausubel, et al. (1987 and Supplements); and Kunkel, et al. (1987) Methods in Enzymol. 154:367-382.

The mutations in the DNA normally should not place coding sequences out of reading frames and preferably will not create complementary regions that could hybridize to produce secondary mRNA structure such as loops or hairpins.

The present invention also provides recombinant proteins, e.g., heterologous fusion proteins using segments from these proteins. A heterologous fusion protein is a fusion of proteins or segments which are naturally not normally fused in the same manner. Thus, the fusion product of an immunoglobulin with a polypeptide is a continuous protein molecule having sequences fused in a typical peptide linkage, typically made as a single

translation product and exhibiting properties derived from each source peptide. A similar concept applies to heterologous nucleic acid sequences.

The present invention also provides recombinant proteins, e.g., heterologous fusion proteins using segments from these proteins. A heterologous fusion protein is a fusion of proteins or segments which are naturally not normally fused in the same manner. A similar concept applies to heterologous nucleic acid sequences. Fusion proteins will be useful as sources for cleaving, separating, and purifying portions thereof.

In addition, new constructs may be made from combining similar functional domains from other proteins. For example, target-binding or other segments may be "swapped" between different new fusion polypeptides or fragments. See, e.g., Cunningham, et al. (1989) Science 243:1330-1336; and O'Dowd, et al. (1988) J. Biol. Chem. 263:15985-15992.

The phosphoramidite method described by Beaucage and Carruthers (1981) Tetra. Letts. 22:1859-1862, will produce suitable synthetic DNA fragments. A double stranded fragment will often be obtained either by synthesizing the complementary strand and annealing the strand together under appropriate conditions or by adding the complementary strand using DNA polymerase with an appropriate primer sequence, e.g., PCR techniques.

IV. Functional Variants

The blocking of physiological response with, e.g., HDTEA84, HSLJD37R, RANKL, HCC5 chemokine, MD-1, or MD-2, may result from the inhibition of binding of the respective ligand to signaling form of receptor or binding counterstructure, e.g., through competitive inhibition. In others, binding affinity to substrate may be modifiable or competed with, e.g., DC-PGT, Dubs, or cyclin E2. Thus, in vitro assays of the present invention will often use isolated protein, soluble fragments comprising ligand or substrate binding segments of these proteins, or forms attached to solid phase substrates. These assays will also allow for the diagnostic determination of the effects of either binding segment mutations

and modifications, or antigen mutations and modifications, e.g., HDTEA84, HSLJD37R, RANKL, MD-1, or MD-2 analogs.

This invention also contemplates the use of competitive drug screening assays, e.g., where neutralizing antibodies to antigen or binding fragments compete with a test compound for binding to the protein, e.g., of natural protein sequence. This is applicable to substrate binding, e.g., competitive inhibitors, and in receptor interaction, where the protein has a binding counterstructure.

"Derivatives" of , e.g., receptor, antigens include amino acid sequence mutants from naturally occurring forms, glycosylation variants, and covalent or aggregate conjugates with other chemical moieties. Covalent derivatives can be prepared by linkage of functionalities to groups which are found in receptor amino acid side chains or at the N- or C- termini, e.g., by standard means. See, e.g., Lundblad and Noyes (1988) Chemical Reagents for Protein Modification, vols. 1-2, CRC Press, Inc., Boca Raton, FL; Hugli (ed. 1989) Techniques in Protein Chemistry, Academic Press, San Diego, CA; and Wong (1991) Chemistry of Protein Conjugation and Cross Linking, CRC Press, Boca Raton, FL.

In particular, glycosylation alterations are included, e.g., made by modifying the glycosylation patterns of a polypeptide during its synthesis and processing, or in further processing steps. See, e.g., Elbein (1987) Ann. Rev. Biochem. 56:497-534. Also embraced are versions of the peptides with the same primary amino acid sequence which have other minor modifications, including phosphorylated amino acid residues, e.g., phosphotyrosine, phosphoserine, or phosphothreonine.

Fusion polypeptides between these proteins and other homologous or heterologous proteins are also provided. Many cytokine receptors or other surface proteins are multimeric, e.g., homodimeric entities, and a repeat construct may have various advantages, including lessened susceptibility to proteolytic cleavage. Typical examples are fusions of a reporter polypeptide, e.g., luciferase, with a segment or domain of a protein, e.g., a receptor-binding segment, so that the presence or location of the fused ligand may be easily determined. See, e.g., Dull, et al.,

U.S. Patent No. 4,859,609. Other gene fusion partners include bacterial ß-galactosidase, trpE, Protein A, ß-lactamase, alpha amylase, alcohol dehydrogenase, yeast alpha mating factor, and detection or purification tags such as a FLAG sequence of His6 sequence. See, e.g., Godowski, et al. (1988) Science 241:812-816. Of particular interest are fusion constructs of receptor with a membrane attachment domain.

Fusion peptides will typically be made by either recombinant nucleic acid methods or by synthetic polypeptide methods. Techniques for nucleic acid manipulation and expression are described generally, e.g., in Sambrook, et al. (1989) Molecular Cloning: A Laboratory Manual (2d ed.), vols. 1-3, Cold Spring Harbor Laboratory; and Ausubel, et al. (eds. 1993) Current Protocols in Molecular Biology, Greene and Wiley, NY. Techniques for synthesis of polypeptides are described, e.g., in Merrifield (1963) J. Amer. Chem. Soc. 85:2149-2156; Merrifield (1986) Science 232: 341-347; Atherton, et al. (1989) Solid Phase Peptide Synthesis: A Practical Approach, IRL Press, Oxford; and Grant (1992) Synthetic Peptides: A User's Guide, W.H. Freeman, NY.

This invention also contemplates the use of derivatives of the proteins other than variations in amino acid sequence or glycosylation. Such derivatives may involve covalent or aggregative association with chemical moieties. Covalent or aggregative derivatives will be useful as immunogens, as reagents in immunoassays, or in purification methods such as for affinity purification of binding partners, e.g., other antigens. The desired proteins can be immobilized by covalent bonding to a solid support such as cyanogen bromide-activated SEPHAROSE, by methods which are well known in the art, or adsorbed onto polyolefin surfaces, with or without glutaraldehyde cross-linking, for use in the assay or purification of antibodies or an alternative binding composition. The protein can also be labeled with a detectable group, e.g., for use in diagnostic assays. Purification may be effected by an immobilized antibody or complementary binding partner. Conversely, immunoabsorption or immunodepletion techniques may be developed.

A solubilized protein or fragment of this invention can be used as an immunogen for the production of antisera or antibodies specific for binding to the antigen or fragments thereof. Purified antigen can be used to screen monoclonal antibodies or antigen-binding fragments, encompassing antigen binding fragments of natural antibodies, e.g., Fab, Fab', $F(ab)_2$, etc. Purified protein can also be used as a reagent to detect antibodies generated in response to the presence of elevated levels of the antigen or cell fragments containing the antigen, both of which may be diagnostic of an abnormal or specific physiological or disease condition. This invention contemplates antibodies raised against amino acid sequences encoded by nucleotide sequences described, or fragments of proteins containing it. In particular, this invention contemplates antibodies having binding affinity to or being raised against specific fragments, e.g., which are predicted to lie outside of the lipid bilayer, both extracellular or intracellular.

The present invention contemplates the isolation of additional closely related species variants. Southern and Northern blot analysis should establish that similar genetic entities exist in other mammals. It is likely that these proteins are widespread in species variants, e.g., rodents, lagomorphs, carnivores, artiodactyla, perissodactyla, and primates.

The invention also provides means to isolate a group of related antigens displaying both distinctness and similarities in structure, expression, and function. Elucidation of many of the physiological effects of the molecules will be greatly accelerated by the isolation and characterization of additional distinct species variants of them. In particular, the present invention provides useful probes for identifying additional homologous genetic entities in different species.

The isolated genes will allow transformation of cells lacking expression of a corresponding protein, e.g., either species types or cells which lack corresponding antigens and exhibit negative background activity. This should allow analysis of the function of genes in comparison to untransformed control cells.

Dissection of critical structural elements which effect the various activation or differentiation functions mediated through these antigens is possible using standard techniques of modern molecular biology, particularly in comparing members of the related class. See, e.g., the homolog-scanning mutagenesis technique described in Cunningham, et al. (1989) Science 243:1339-1336; and approaches used in O'Dowd, et al. (1988) J. Biol. Chem. 263:15985-15992; and Lechleiter, et al. (1990) EMBO J. 9:4381-4390.

The invention also provides, in the context of the DC-PGT, means to isolate a group of related organic anion transporters, e.g., other vertebrate prostaglandin transporters, displaying both distinctness and similarities in structure, expression, and function. Elucidation of many of the physiological effects of the antigens will be greatly accelerated by the isolation and characterization of distinct species variants. In particular, the present invention provides useful probes for identifying additional homologous genetic entities in different species. The results described above indicate that sufficiently homologous genes exist in other species that cross-species hybridization is likely to allow successful cloning.

The isolated genes will allow transformation of cells lacking expression of a described gene, e.g., prostaglandin transporter. Various species types or cells which lack corresponding proteins can be isolated, and should exhibit negative background activity. Expression of transformed genes will allow isolation of antigenically pure cell lines, with defined or single specie variants. This approach will allow for more sensitive detection and discrimination of the physiological effects of the gene, e.g., prostaglandin transporters. Subcellular fragments, e.g., cytoplasts or membrane fragments, can be isolated and used.

The DC-PGT genes may also be useful to increase the rate of transport of desired prostaglandins into transformed cells. Thus, the transporter may be transformed into cells for targeting of incorporation of desired substrates or analogs. For instance, it may be useful to incorporate specific modified prostaglandins into those cells, which may become more susceptible to other

treatments, or directly affected. Thus, specific dendritic cell subsets may be transformed to become more sensitive to prostaglandins or specific substrates. Conversely, such cells may be useful screening targets to identify entities which can block transport, thereby preventing uptake of substrate.

Structural studies of the transporter will lead to design of new variants, particularly analogs exhibiting modified binding affinity, or perhaps, altered rate of transporter activity. This can be combined with previously described screening methods to isolate variants exhibiting desired spectra of activities. Alternatively, many different prostaglandins and analogs thereof may be screened for either transporter binding affinity or transporter transfer. The transporter may require a direct energy source, e.g., ATP or other nucleotide triphosphate, or may depend upon an ion gradient, as described above.

In the context of the Dubs and cyclin E2, intracellular functions would probably involve segments of the antigen which are normally accessible to the cytosol, as would segments of the receptors. However, protein internalization may occur under certain circumstances, and interaction between intracellular components and "extracellular" components may occur. The specific segments of interaction of protein with other intracellular components may be identified by mutagenesis or direct biochemical means, e.g., cross-linking or affinity methods.

Structural analysis by crystallographic or other physical methods will also be applicable. Further investigation of the mechanism of signal transduction will include study of associated components which may be isolatable by affinity methods or by genetic means, e.g., complementation analysis of mutants.

Further study of the expression and control of the proteins will be pursued. The controlling elements associated with the antigens should exhibit differential physiological, developmental, tissue specific, or other expression patterns. Upstream or downstream genetic regions, e.g., control elements, are of interest. In particular, physiological or developmental variants, e.g., multiple alternatively processed forms of the antigen might be found. Thus, differential splicing of message may lead to an

assortment of membrane bound forms, soluble forms, and modified versions of antigen.

Structural studies of the antigens will lead to design of new antigens, particularly analogs exhibiting agonist or antagonist properties on the molecule. This can be combined with previously described screening methods to isolate antigens exhibiting desired spectra of activities.

V. Antibodies

Antibodies can be raised to the various described polypeptides, including species, polymorphic, or allelic variants, and fragments thereof, both in their naturally occurring forms and in their recombinant forms. Additionally, antibodies can be raised to the proteins in either their active forms or in their inactive forms, including native or denatured versions. Anti-idiotypic antibodies are also contemplated.

Antibodies, including binding fragments and single chain versions, against predetermined fragments of the antigens can be raised by immunization of animals with conjugates of the fragments with immunogenic proteins. Monoclonal antibodies are prepared from cells secreting the desired antibody. These antibodies can be screened for binding to normal or defective polypeptide, or screened for agonistic or antagonistic activity. Antibodies may be agonistic or antagonistic, e.g., by sterically blocking partner or substrate binding. These monoclonal antibodies will usually bind with at least a K_D of about 1 mM, more usually at least about 300 μM, typically at least about 100 μM, more typically at least about 30 μM, preferably at least about 10 μM, and more preferably at least about 3 μM or better. More preferred embodiments may have even higher affinities, e.g., at least 300 nM, 30 nM, 3 nM, or perhaps even picomolar affinity.

The term "binding composition" refers to molecules that bind with affinity and selectivity to, e.g., the DC-PGT, e.g., in an antibody-antigen interaction. However, other compounds, e.g., accessory proteins, may also specifically and/or selectively associate with the antigen to the exclusion of other molecules. Typically, the association will be in a natural physiologically

relevant protein-protein interaction, either covalent or non-covalent, and may include members of a multiprotein complex, including carrier compounds or dimerization partners. The molecule may be a polymer, or chemical reagent. No implication as to whether an antigen is necessarily a convex shaped molecule, e.g., the ligand or the receptor of a ligand-receptor interaction, is necessarily represented, other than whether the interaction exhibits similar specificity, e.g., specific or selective affinity. A functional analog may be a polypeptide with structural modifications, e.g., a mutein, or may be a wholly unrelated molecule, e.g., which has a molecular shape which interacts with the appropriate ligand binding determinants. The ligands may serve as agonists or antagonists of the receptor, see, e.g., Goodman, et al. Goodman & Gilman's: The Pharmacological Bases of Therapeutics (current edition) Pergamon Press, Tarrytown, N.Y.

The term "binding agent:antigen complex", as used herein, refers to a complex of a binding agent and antigen, e.g., a DC-PGT protein, that is formed by specific binding of the binding agent to antigen. Specific or selective binding of the binding agent means that the binding agent has a specific binding site, e.g., antigen binding site, that recognizes a site on the antigen. For example, antibodies raised to a DC-PGT protein and recognizing an epitope on the protein are capable of forming a binding agent:DC-PGT protein complex by specific selective binding. Typically, the formation of a binding agent:DC-PGT protein complex allows the qualitative or quantitative measurement of DC-PGT protein in a mixture of other proteins and biologics. The term "antibody:DC-PGT protein complex" refers to an embodiment in which the binding agent, e.g., is the antigen binding portion from an antibody. The antibody may be monoclonal, polyclonal, or a binding fragment of an antibody, e.g., an Fab or F(ab)2 fragment. The antibody will preferably be a polyclonal antibody for cross-reactivity testing purposes.

The phrase "specifically binds to an antibody" or "specifically immunoreactive with", when referring to a protein or peptide, refers to a binding reaction which is determinative of

the presence of the protein in the presence of a heterogeneous population of other proteins and other biological components. Thus, under designated immunoassay conditions, the specified antibodies bind to a particular protein and do not significantly bind other proteins present in the sample. Specific binding to an antibody under such conditions may require an antibody that is selected for its specificity or selectivity for a particular protein. Often, the serum can be immunoselected or immunodepleted, to minimize crossreactivity with a specific target protein.

A DC-PGT polypeptide that specifically binds to, or that is specifically immunoreactive with, an antibody, e.g., such as a polyclonal antibody, generated against a defined immunogen, e.g., such as an immunogen consisting of an amino acid sequence of SEQ ID NO: 2, or fragments thereof, or a polypeptide generated from the nucleic acid of SEQ ID NO: 1 is typically determined in an immunoassay. Included within the metes and bounds of the present invention are those nucleic acid sequences described herein, including functional variants, that encode polypeptides that selectively bind to polyclonal antibodies generated against the prototypical DC-PGT polypeptide as structurally and functionally defined herein. The immunoassay typically uses a polyclonal antiserum which was raised, e.g., to a protein of SEQ ID NO: 2. This antiserum is selected to have low crossreactivity against appropriate other PGT family members, preferably from the same species, and any such crossreactivity is removed by immunoabsorption prior to use in the immunoassay. Appropriate selective serum preparations can be isolated, and characterized.

The purified protein or defined peptides are useful for generating antibodies by standard methods, as described above. Synthetic peptides or purified protein can be presented to an immune system to generate monoclonal or polyclonal antibodies. See, e.g., Coligan (1991) Current Protocols in Immunology Wiley/Greene; and Harlow and Lane (1989) Antibodies: A Laboratory Manual, Cold Spring Harbor Press. Alternatively, the HDTEA84 can be used as a specific binding reagent, and advantage can be taken

of its specificity of binding, much like an antibody would be used.

For example, the specific binding composition could be used for screening of an expression library made from a cell line which expresses an HDTEA84, HSLJD37R, or RANKL. The screening can be standard staining of surface expressed antigen constructs, or by panning. Screening of intracellular expression can also be performed by various staining or immunofluorescence procedures. The binding compositions could be used to affinity purify or sort out cells expressing the protein.

In order to produce antisera for use in an immunoassay, the protein, e.g., of SEQ ID NO: 2, is isolated as described herein. For example, recombinant protein may be produced in a mammalian cell line. An appropriate host, e.g., an inbred strain of mice such as Balb/c, is immunized with the protein of SEQ ID NO: 2 using a standard adjuvant, such as Freund's adjuvant, and a standard mouse immunization protocol (see Harlow and Lane). Alternatively, a substantially full length synthetic peptide derived from the sequences disclosed herein can be used as an immunogen. Polyclonal sera are collected and titered against the immunogen protein in an immunoassay, e.g., a solid phase immunoassay with the immunogen immobilized on a solid support. Polyclonal antisera with a titer of 10^4 or greater are selected and tested for their cross reactivity against other PGT family members, e.g., human or rat PGT, using a competitive binding immunoassay such as the one described in Harlow and Lane, supra, at pages 570-573. Preferably at least two PGT family members are used in this determination in conjunction with the target. These PGT family members can be produced as recombinant proteins and isolated using standard molecular biology and protein chemistry techniques as described herein. Thus, antibody preparations can be identified or produced having desired selectivity or specificity for subsets of PGT family members.

Immunoassays in the competitive binding format can be used for the crossreactivity determinations. For example, the protein of SEQ ID NO: 2 can be immobilized to a solid support. Proteins added to the assay compete with the binding of the antisera to the

immobilized antigen. The ability of the above proteins to compete with the binding of the antisera to the immobilized protein is compared to the protein of SEQ ID NO: 2. The percent crossreactivity for the above proteins is calculated, using standard calculations. Those antisera with less than 10% crossreactivity with each of the proteins listed above are selected and pooled. The cross-reacting antibodies are then removed from the pooled antisera by immunoabsorption or immunodepletion with the above-listed proteins.

The immunoabsorbed and pooled antisera are then used in a competitive binding immunoassay as described above to compare a second protein to the immunogen protein. In order to make this comparison, the two proteins are each assayed at a wide range of concentrations and the amount of each protein required to inhibit 50% of the binding of the antisera to the immobilized protein is determined. If the amount of the second protein required is less than twice the amount of the protein of, e.g., SEQ ID NO: 2 that is required, then the second protein is said to specifically bind to an antibody generated to the immunogen.

The antibodies of this invention can also be useful in diagnostic applications. As capture or non-neutralizing antibodies, they can be screened for ability to bind to the antigens without inhibiting binding by a partner. As neutralizing antibodies, they can be useful in competitive binding assays. They will also be useful in detecting or quantifying a described protein or its binding partners. See, e.g., Chan (ed. 1987) Immunology: A Practical Guide, Academic Press, Orlando, FL; Price and Newman (eds. 1991) Principles and Practice of Immunoassay, Stockton Press, N.Y.; and Ngo (ed. 1988) Nonisotopic Immunoassay, Plenum Press, N.Y. Cross absorptions or depletions and other tests will identify antibodies which exhibit various spectra of specificities, e.g., unique or shared species specificities.

Further, the antibodies, including antigen binding fragments, of this invention can be potent antagonists that bind to the antigen and inhibit functional binding or inhibit the ability of a binding partner to elicit a biological response. They also can be useful as non-neutralizing antibodies and can be coupled to toxins

or radionuclides so that when the antibody binds to antigen, a cell expressing it, e.g., on its surface, is killed. Further, these antibodies can be conjugated to drugs or other therapeutic agents, either directly or indirectly by means of a linker, and may effect drug targeting. They may be labeled for histology evaluation.

Antigen fragments may be joined to other materials, particularly polypeptides, as fused or covalently joined polypeptides to be used as immunogens. An antigen and its fragments may be fused or covalently linked to a variety of immunogens, such as keyhole limpet hemocyanin, bovine serum albumin, tetanus toxoid, etc. See Microbiology, Hoeber Medical Division, Harper and Row, 1969; Landsteiner (1962) Specificity of Serological Reactions, Dover Publications, New York; Williams, et al. (1967) Methods in Immunology and Immunochemistry, vol. 1, Academic Press, New York; and Harlow and Lane (1988) Antibodies: A Laboratory Manual, CSH Press, NY, for descriptions of methods of preparing polyclonal antisera.

In some instances, it is desirable to prepare monoclonal antibodies from various mammalian hosts, such as mice, rodents, primates, humans, etc. Description of techniques for preparing such monoclonal antibodies may be found in, e.g., Stites, et al. (eds.) Basic and Clinical Immunology (4th ed.), Lange Medical Publications, Los Altos, CA, and references cited therein; Harlow and Lane (1988) Antibodies: A Laboratory Manual, CSH Press; Goding (1986) Monoclonal Antibodies: Principles and Practice (2d ed.), Academic Press, New York; and particularly in Kohler and Milstein (1975) in Nature 256:495-497, which discusses one method of generating monoclonal antibodies.

Other suitable techniques involve in vitro exposure of lymphocytes to the antigenic polypeptides or alternatively to selection of libraries of antibodies in phage or similar vectors. See, Huse, et al. (1989) "Generation of a Large Combinatorial Library of the Immunoglobulin Repertoire in Phage Lambda," Science 246:1275-1281; and Ward, et al. (1989) Nature 341:544-546. The polypeptides and antibodies of the present invention may be used

with or without modification, including chimeric or humanized antibodies. Frequently, the polypeptides and antibodies will be labeled by joining, either covalently or non-covalently, a substance which provides for a detectable signal. A wide variety of labels and conjugation techniques are known and are reported extensively in both the scientific and patent literature. Suitable labels include radionuclides, enzymes, substrates, cofactors, inhibitors, fluorescent moieties, chemiluminescent moieties, magnetic particles, and the like. Patents, teaching the use of such labels include U.S. Patent Nos. 3,817,837; 3,850,752; 3,939,350; 3,996,345; 4,277,437; 4,275,149; and 4,366,241. Also, recombinant immunoglobulins may be produced, see Cabilly, U.S. Patent No. 4,816,567; Moore, et al., U.S. Patent No. 4,642,334; and Queen, et al. (1989) Proc. Nat'l Acad. Sci. USA 86:10029-10033.

The antibodies of this invention can also be used for affinity chromatography in isolating the protein. Columns can be prepared where the antibodies are linked to a solid support, e.g., particles, such as agarose, Sephadex, or the like, where a cell lysate may be passed through the column, the column washed, followed by increasing concentrations of a mild denaturant, whereby the purified protein will be released. See, e.g., Wilchek et al. (1984) Meth. Enzymol. 104:3-55.

Antibodies raised against each protein will also be useful to raise anti-idiotypic antibodies. These will be useful in detecting or diagnosing various immunological conditions related to expression of the respective antigens.

VI. Nucleic Acids

The described peptide sequences and the related reagents are useful in detecting, isolating, or identifying a DNA clone encoding, e.g., the DC-PGT, HDTEA84, HSLJD37R, RANKL, HCC5, Dub11, Dub12, MD-1, MD-2, or cyclin E2 polypeptides, e.g., from a natural source. Typically, the nucleic acids, particularly natural genes, will be useful in isolating a gene from mammal, and similar procedures will be applied to isolate genes from other species, e.g., warm blooded animals, such as birds and mammals. They will

be useful for isolating genes from domestic pets, e.g., dogs and cats, and livestock, e.g., horse, pigs, cattle, sheep, chickens, turkeys, fish, etc. Cross hybridization will allow isolation of respective counterpart genes from other species. A number of different approaches should be available to successfully isolate a suitable nucleic acid clone.

The peptide sequences allow preparation of peptides to generate antibodies to recognize such segments, and various different methods may be used to prepare such peptides. As used herein, e.g., the term prostaglandin transporter shall encompass, when used in a protein context, a protein having an amino acid sequence shown in Table 1, or a significant fragment of such a protein. It also refers to a vertebrate, e.g., mammal, including human, derived polypeptide which exhibits similar biological function, e.g., antigenic, or interacts with prostaglandin transporter specific binding components, e.g., specific antibodies. These binding components, e.g., antibodies, typically bind to a prostaglandin transporter with high affinity, e.g., at least about 100 nM, usually better than about 30 nM, preferably better than about 10 nM, and more preferably at better than about 3 nM. Still higher affinities are possible, e.g., 100 pM, 30 pM, 100 fM, etc.

This invention contemplates use of isolated DNA or fragments of the present invention to encode a structurally related, e.g., antigenically related, or biologically active protein, e.g., substrate binding or transporting, prostaglandin transporter, TNF receptor-like proteins, chemokine, Dubs, surface receptors, or cell cycle regulatory proteins, or polypeptide fragments thereof. In addition, this invention covers isolated or recombinant DNA which encodes a structurally related or biologically active protein or polypeptide and that is capable of hybridizing under appropriate conditions with the DNA sequences described herein. Said biologically active protein or polypeptide can be an intact antigen, or fragment, and have an amino acid sequence as disclosed in Tables 1-13. Further, this invention covers the use of isolated or recombinant DNA, or fragments thereof, which encode proteins which are homologous to the respective genes or which

were isolated using cDNA encoding the proteins as a probe. Preferably such homologous genes or proteins will be natural forms isolated from other vertebrates, e.g., warm blooded animals, including mammals, such as primates. The isolated DNA can have the respective regulatory sequences in the 5' and 3' flanks, e.g., promoters, enhancers, poly-A addition signals, and others.

An "isolated" nucleic acid is a nucleic acid, e.g., an RNA, DNA, or a mixed polymer, which is substantially separated from other components which naturally accompany a native sequence, e.g., ribosomes, polymerases, and flanking genomic sequences from the originating species. The term embraces a nucleic acid sequence which has been removed from its naturally occurring intracellular environment, and includes recombinant or cloned DNA isolates and chemically synthesized analogs or analogs biologically synthesized by heterologous systems. A substantially pure molecule includes once or currently isolated forms of the molecule. Alternatively, a purified species may be separated from host components from a recombinant expression system. Generally, the nucleic acid will be in a vector or fragment less than about 50 kb, usually less than about 30 kb, typically less than about 10 kb, and preferably less than about 6 kb.

An isolated nucleic acid will generally be a homogeneous composition of molecules, but will, in some embodiments, contain minor heterogeneity. This heterogeneity is typically found at the polymer ends or portions not critical to a desired biological function or activity.

The peptide segments can also be used to predict appropriate oligonucleotides to screen a library. The genetic code, e.g., reverse translation, can be used to select appropriate oligonucleotides useful as probes for screening. See, e.g., SEQ ID NO: 1, 5, 7, 9, 11, 16, 18, 20, 22, 24, 31, 33, 35, 37, 41, 43, 47, or 53. In combination with polymerase chain reaction (PCR) techniques, synthetic oligonucleotides will be useful in selecting correct clones from a library. Complementary sequences will also be used as probes, primers, or antisense strands. Various fragments should be particularly useful, e.g., coupled with

anchored vector or poly-A complementary PCR techniques or with complementary DNA of other peptides.

This invention contemplates use of isolated DNA or fragments to encode a biologically active corresponding polypeptide. In addition, this invention covers isolated or recombinant DNA which encodes a biologically active protein or polypeptide which is capable of hybridizing under appropriate conditions with the DNA sequences described herein. Said biologically active protein or polypeptide can be an intact antigen, or fragment, and have an amino acid sequence disclosed in, e.g., SEQ ID NO: 2, 6, 8, 10, 12, 17, 19, 21, 23, 25, 32, 34, 36, 38, 42, 44, 46, 48, 49, or 54. Further, this invention covers the use of isolated or recombinant DNA, or fragments thereof, which encode proteins which are homologous to a described protein or which was isolated using cDNA encoding such protein as a probe. The isolated DNA can have the respective regulatory sequences in the 5' and 3' flanks, e.g., promoters, enhancers, poly-A addition signals, and others.

A "recombinant" nucleic acid is defined either by its method of production or its structure. In reference to its method of production, e.g., a product made by a process, the process is use of recombinant nucleic acid techniques, e.g., involving human intervention in the nucleotide sequence, typically selection or production. Alternatively, it can be a nucleic acid made by generating a sequence comprising fusion of two fragments which are not naturally contiguous to each other, but is meant to exclude products of nature, e.g., naturally occurring mutants. Thus, e.g., products made by transforming cells with any unnaturally occurring vector is encompassed, as are nucleic acids comprising sequence derived using any synthetic oligonucleotide process. Such is often done to replace a codon with a redundant codon encoding the same or a conservative amino acid, while typically introducing or removing a sequence recognition site.

Alternatively, it is performed to join together nucleic acid segments of desired functions to generate a single genetic entity comprising a desired combination of functions not found in the commonly available natural forms. Restriction enzyme recognition sites are often the target of such artificial manipulations, but

other site specific targets, e.g., promoters, DNA replication sites, regulation sequences, control sequences, or other useful features may be incorporated by design. A similar concept is intended for a recombinant, e.g., fusion, polypeptide. Specifically included are synthetic nucleic acids which, by genetic code redundancy, encode polypeptides similar to fragments of these antigens, and fusions of sequences from various different species variants.

A significant "fragment" in a nucleic acid context is a contiguous segment of at least about 17 nucleotides, generally at least about 22 nucleotides, ordinarily at least about 29 nucleotides, more often at least about 35 nucleotides, typically at least about 41 nucleotides, usually at least about 47 nucleotides, preferably at least about 55 nucleotides, and in particularly preferred embodiments will be at least about 60 or more nucleotides.

A DNA which codes for a DC-PGT, HDTEA84, HSLJD37R, RANKL, HCC5, Dub, MD-1, MD-2, or cyclin E2 protein will be particularly useful to identify genes, mRNA, and cDNA species which code for related or homologous proteins, as well as DNAs which code for homologous proteins from different species. There are likely homologs in other species, including primates, rodents, birds, and fish. Various such proteins should be homologous and are encompassed herein. However, even genes encoding proteins that have a more distant evolutionary relationship to the antigen can readily be isolated under appropriate conditions using these sequences if they are sufficiently homologous. Primate proteins are of particular interest.

Recombinant clones derived from the genomic sequences, e.g., containing introns, will be useful for transgenic studies, including, e.g., transgenic cells and organisms, and for gene therapy. See, e.g., Goodnow (1992) "Transgenic Animals" in Roitt (ed.) Encyclopedia of Immunology, Academic Press, San Diego, pp. 1502-1504; Travis (1992) Science 256:1392-1394; Kuhn, et al. (1991) Science 254:707-710; Capecchi (1989) Science 244:1288; Robertson (1987 ed.) Teratocarcinomas and Embryonic Stem Cells: A

Practical Approach, IRL Press, Oxford; and Rosenberg (1992) J. Clinical Oncology 10:180-199.

Substantial homology in the nucleic acid sequence comparison context means either that the segments, or their complementary strands, when compared, are identical when optimally aligned, with appropriate nucleotide insertions or deletions, in at least about 50% of the nucleotides, generally at least about 58%, ordinarily at least about 65%, often at least about 71%, typically at least about 77%, usually at least about 85%, preferably at least about 95 to 98% or more, and in particular embodiments, as high as about 99% or more of the nucleotides. Alternatively, substantial homology exists when the segments will hybridize under selective hybridization conditions, to a strand, or its complement, typically using a sequence of DC-PGT, e.g., in SEQ ID NO: 1. Typically, selective hybridization will occur when there is at least about 55% homology over a stretch of at least about 30 nucleotides, preferably at least about 75% over a stretch of about 25 nucleotides, and most preferably at least about 90% over about 20 nucleotides. See, Kanehisa (1984) Nuc. Acids Res. 12:203-213. The length of homology comparison, as described, may be over longer stretches, and in certain embodiments will be over a stretch of at least about 17 nucleotides, usually at least about 28 nucleotides, typically at least about 40 nucleotides, and preferably at least about 75 to 100 or more nucleotides.

Stringent conditions, in referring to homology in the hybridization context, will be stringent combined conditions of salt, temperature, organic solvents, and other parameters, typically those controlled in hybridization reactions. Stringent temperature conditions will usually include temperatures in excess of about 30° C, usually in excess of about 37° C, typically in excess of about 55° C, preferably in excess of about 70° C. Stringent salt conditions will ordinarily be less than about 1000 mM, usually less than about 400 mM, typically less than about 250 mM, preferably less than about 150 mM. However, the combination of parameters is much more important than the measure of any single parameter. See, e.g., Wetmur and Davidson (1968) J. Mol. Biol. 31:349-370. Hybridization under stringent conditions should

give a background of at least 2-fold over background, preferably at least 3-5 or more.

DC-PGT, HDTEA84, HSLJD37R, RANKL, HCC5, Dub11, Dub12, MD-1, MD-2, or cyclin E2 from other mammalian species can be cloned and isolated by cross-species hybridization of closely related species. Homology may be relatively low between distantly related species, and thus hybridization of relatively closely related species is advisable. Alternatively, preparation of an antibody preparation which exhibits less species specificity may be useful in expression cloning approaches.

VII. Making Proteins; Mimetics

Nucleic acids which encodes the described proteins, or fragments thereof, can be obtained by chemical synthesis, screening cDNA libraries, or screening genomic libraries prepared from a wide variety of cell lines or tissue samples. See, e.g., Okayama and Berg (1982) Mol. Cell. Biol. 2:161-170; Gubler and Hoffman (1983) Gene 25:263-269; and Glover (ed. 1984) DNA Cloning: A Practical Approach, IRL Press, Oxford. Alternatively, the sequences provided herein provide useful PCR primers or allow synthetic or other preparation of suitable genes encoding a receptor; including, naturally occurring embodiments.

DNA can be expressed in a wide variety of host cells for the synthesis of a full-length protein, or fragments, which can in turn, e.g., be used to generate polyclonal or monoclonal antibodies; for binding studies; for construction and expression of modified molecules; for structure/function studies; and for controls in detection assays. Each antigen or its fragments can be expressed in host cells that are transformed or transfected with appropriate expression vectors. These molecules can be substantially purified to be free of protein or cellular contaminants, other than those derived from the recombinant host, and therefore are particularly useful in pharmaceutical compositions when combined with a pharmaceutically acceptable carrier and/or diluent. The antigen, or portions thereof, may be expressed as fusions with other proteins.

Vectors, as used herein, comprise plasmids, viruses, bacteriophage, integratable DNA fragments, and other vehicles which enable the integration of DNA fragments into the genome of the host. See, e.g., Pouwels, et al. (1985 and Supplements) Cloning Vectors: A Laboratory Manual, Elsevier, N.Y.; and Rodriguez, et al. (1988 eds.) Vectors: A Survey of Molecular Cloning Vectors and Their Uses, Buttersworth, Boston, MA. Expression vectors are typically self-replicating DNA or RNA constructs containing the desired antigen gene or its fragments, usually operably linked to suitable genetic control elements that are recognized in a suitable host cell. These control elements are capable of effecting expression within a suitable host. The specific type of control elements necessary to effect expression will depend upon the eventual host cell used. Generally, the genetic control elements can include a prokaryotic promoter system or a eukaryotic promoter expression control system, and typically include a transcriptional promoter, an optional operator to control the onset of transcription, transcription enhancers to elevate the level of mRNA expression, a sequence that encodes a suitable ribosome binding site, and sequences that terminate transcription and translation. Expression vectors also usually contain an origin of replication that allows the vector to replicate independently of the host cell.

For purposes of this invention, DNA sequences are operably linked when they are functionally related to each other. For example, DNA for a presequence or secretory leader is operably linked to a polypeptide if it is expressed as a preprotein or participates in directing the polypeptide to the cell membrane or in secretion of the polypeptide. A promoter is operably linked to a coding sequence if it controls the transcription of the polypeptide; a ribosome binding site is operably linked to a coding sequence if it is positioned to permit translation. Usually, operably linked means contiguous and in reading frame, however, certain genetic elements such as repressor genes are not contiguously linked but still bind to operator sequences that in turn control expression. See e.g., Rodriguez, et al., Chapter 10, pp. 205-236; Balbas and Bolivar (1990) Methods in Enzymol. 185:14-

37; and Ausubel, et al. (1993) Current Protocols in Molecular Biology, Greene and Wiley, NY.

Representative examples of suitable expression vectors include pCDNA1; pCD, see Okayama, et al. (1985) Mol. Cell Biol. 5:1136-1142; pMC1neo Poly-A, see Thomas, et al. (1987) Cell 51:503-512; and a baculovirus vector such as pAC 373 or pAC 610. See, e.g., Miller (1988) Ann. Rev. Microbiol. 42:177-199. Usually, expression vectors are designed for stable replication in their host cells or for amplification to greatly increase the total number of copies of the desirable gene per cell. It is not always necessary to require that an expression vector replicate in a host cell, e.g., it is possible to effect transient expression of the antigen or its fragments in various hosts using vectors that do not contain a replication origin that is recognized by the host cell. It is also possible to use vectors that cause integration of a gene or its fragments into the host DNA by recombination, or to integrate a promoter which controls expression of an endogenous gene.

Adenovirus techniques are available for expression of the genes in various cells and organs. See, e.g., Hitt, et al. (1997) Adv. Pharmacol. 40:137-195; and literature from Quantum Biotechnologies, Montreal, Canada. Animals may be useful to determine the effects of the gene on various developmental or physiologically functional animal systems.

Suitable host cells include prokaryotes, lower eukaryotes, and higher eukaryotes. Prokaryotes include both gram negative and gram positive organisms, e.g., E. coli and B. subtilis. Lower eukaryotes include yeasts, e.g., S. cerevisiae and Pichia, and species of the genus Dictyostelium. Higher eukaryotes include established tissue culture cell lines from animal cells, both of non-mammalian origin, e.g., insect cells, and birds, and of mammalian origin, e.g., human, primates, and rodents.

Prokaryotic host-vector systems include a wide variety of vectors for many different species. As used herein, E. coli and its vectors will be used generically to include equivalent vectors used in other prokaryotes. A representative vector for amplifying DNA is pBR322 or many of its derivatives. Vectors that can be

used to express the prostaglandin transporter or its fragments include, but are not limited to, such vectors as those containing the lac promoter (pUC-series); trp promoter (pBR322-trp); Ipp promoter (the pIN-series); lambda-pP or pR promoters (pOTS); or hybrid promoters such as ptac (pDR540). See Brosius et al. (1988) "Expression Vectors Employing Lambda-, trp-, lac-, and Ipp-derived Promoters", in Rodriguez and Denhardt (eds.) Vectors: A Survey of Molecular Cloning Vectors and Their Uses, Buttersworth, Boston, Chapter 10, pp. 205-236, which is incorporated herein by reference.

Lower eukaryotes, e.g., yeasts and Dictyostelium, may be transformed with vectors encoding vertebrate prostaglandin transporters. For purposes of this invention, the most common lower eukaryotic host is the baker's yeast, Saccharomyces cerevisiae. It will be used to generically represent lower eukaryotes although a number of other strains and species are also available. Yeast vectors typically consist of a replication origin (unless of the integrating type), a selection gene, a promoter, DNA encoding the desired protein or its fragments, and sequences for translation termination, polyadenylation, and transcription termination. Suitable expression vectors for yeast include such constitutive promoters as 3-phosphoglycerate kinase and various other glycolytic enzyme gene promoters or such inducible promoters as the alcohol dehydrogenase 2 promoter or metallothionine promoter. Suitable vectors include derivatives of the following types: self-replicating low copy number (such as the YRp-series), self-replicating high copy number (such as the YEp-series); integrating types (such as the YIp-series), or mini-chromosomes (such as the YCp-series).

Higher eukaryotic tissue culture cells are the preferred host cells for expression of the functionally active prostaglandin transporter. In principle, most higher eukaryotic tissue culture cell lines are workable, e.g., insect baculovirus expression systems, whether from an invertebrate or vertebrate source. However, mammalian cells are preferred, in that the processing, both cotranslationally and posttranslationally is more likely to simulate natural forms. Transformation or transfection and

propagation of such cells has become a routine procedure. Examples of useful cell lines include HeLa cells, Chinese hamster ovary (CHO) cell lines, baby rat kidney (BRK) cell lines, insect cell lines, bird cell lines, and monkey (COS) cell lines. Expression vectors for such cell lines usually include an origin of replication, a promoter, a translation initiation site, RNA splice sites (if genomic DNA is used), a polyadenylation site, and a transcription termination site. These vectors also usually contain a selection gene or amplification gene. Suitable expression vectors may be plasmids, viruses, or retroviruses carrying promoters derived, e.g., from such sources as from adenovirus, SV40, parvoviruses, vaccinia virus, or cytomegalovirus. Representative examples of suitable expression vectors include pCDNA1; pCD, see Okayama et al. (1985) Mol. Cell Biol. 5:1136-1142; pMC1neo Poly-A, see Thomas et al. (1987) Cell 51:503-512; and a baculovirus vector such as pAC 373 or pAC 610.

It will often be desired to express a DC-PGT, HDTEA84, HSLJD37R, RANKL, HCC5, Dub11, Dub12, MD-1, MD-2, or cyclin E2 polypeptide in a system which provides a specific or defined glycosylation pattern. See, e.g., Luckow and Summers (1988) Bio/Technology 6:47-55; and Kaufman (1990) Meth. Enzymol. 185:487-511. Preferred prokaryotic forms lack eukaryotic glycosylation patterns. However, the pattern will be modifiable by exposing the polypeptide, e.g., an unglycosylated form, to appropriate glycosylating proteins introduced into a heterologous expression system. For example, the desired gene may be cotransformed with one or more genes encoding mammalian or other glycosylating enzymes. Using this approach, certain mammalian glycosylation patterns will be achievable or approximated in prokaryote or other cells.

The DC-PGT, HDTEA84, HSLJD37R, RANKL, HCC5, Dub11, Dub12, MD-1, MD-2, or cyclin E2, or a fragment thereof, may be engineered to be phosphatidyl inositol (PI) linked to a cell membrane, but can be removed from membranes by treatment with a phosphatidyl inositol cleaving enzyme, e.g., phosphatidyl inositol phospholipase-C. This releases the antigen in a biologically active form, and allows purification by standard procedures of

protein chemistry. See, e.g., Low (1989) Biochim. Biophys. Acta 988:427-454; Tse, et al. (1985) Science 230:1003-1008; and Brunner, et al. (1991) J. Cell Biol. 114:1275-1283.

Transformed cells include cells, preferably mammalian, that have been transformed or transfected with vectors containing a prostaglandin transporter gene, typically constructed using recombinant DNA techniques. Transformed host cells usually express the antigen or its fragments, but for purposes of cloning, amplifying, and manipulating its DNA, do not need to express the protein. This invention further contemplates culturing transformed cells in a nutrient medium, thus permitting the protein, or soluble fragments, to accumulate in the culture. Soluble protein can be recovered, either from the culture or from the culture medium, and membrane associated proteins may be prepared from suitable cell subfractions.

Now that the genes have been characterized, fragments or derivatives thereof can be prepared by conventional processes for synthesizing peptides. These include processes such as are described in Stewart and Young (1984) Solid Phase Peptide Synthesis, Pierce Chemical Co., Rockford, IL; Bodanszky and Bodanszky (1984) The Practice of Peptide Synthesis, Springer-Verlag, New York; and Bodanszky (1984) The Principles of Peptide Synthesis, Springer-Verlag, New York. For example, an azide process, an acid chloride process, an acid anhydride process, a mixed anhydride process, an active ester process (for example, p-nitrophenyl ester, N-hydroxysuccinimide ester, or cyanomethyl ester), a carbodiimidazole process, an oxidative-reductive process, or a dicyclohexylcarbodiimide (DCCD)/additive process can be used. Solid phase and solution phase syntheses are both applicable to the foregoing processes.

The proteins, fragments, or derivatives are suitably prepared in accordance with the above processes as typically employed in peptide synthesis, generally either by a so-called stepwise process which comprises condensing an amino acid to the terminal amino acid, one by one in sequence, or by coupling peptide fragments to the terminal amino acid. Amino groups that are not

being used in the coupling reaction are typically protected to prevent coupling at an incorrect location.

If a solid phase synthesis is adopted, the C-terminal amino acid is bound to an insoluble carrier or support through its carboxyl group. The insoluble carrier is not particularly limited as long as it has a binding capability to a reactive carboxyl group. Examples of such insoluble carriers include halomethyl resins, such as chloromethyl resin or bromomethyl resin, hydroxymethyl resins, phenol resins, tert-alkyloxycarbonyl-hydrazidated resins, and the like.

An amino group-protected amino acid is bound in sequence through condensation of its activated carboxyl group and the reactive amino group of the previously formed peptide or chain, to synthesize the peptide step by step. After synthesizing the complete sequence, the peptide is split off from the insoluble carrier to produce the peptide. This solid-phase approach is generally described by Merrifield et al. (1963) in J. Am. Chem. Soc. 85:2149-2156, which is incorporated herein by reference.

The prepared protein and fragments thereof can be isolated and purified from the reaction mixture by means of peptide separation, e.g., by extraction, precipitation, electrophoresis and various forms of chromatography, and the like. The proteins of this invention can be obtained in varying degrees of purity depending upon its desired use. Purification can be accomplished by use of the protein purification techniques disclosed herein or by the use of the antibodies herein described in immunoabsorbent affinity chromatography. This immunoabsorbent affinity chromatography is carried out by first linking the antibodies to a solid support and then contacting the linked antibodies with solubilized lysates of appropriate source cells, lysates of other cells expressing the protein, or lysates or supernatants of cells producing the desired protein as a result of DNA techniques, see below. Detergents may be necessary to include in the methods to maintain protein solubility.

VIII. Uses

The present invention provides reagents which will find use in diagnostic applications as described elsewhere herein, e.g., in the general description for cell mediated conditions, or below in the description of kits for diagnosis. The genes will be useful in forensic analyses, e.g., to identify species, or to diagnose different cell subsets or types.

If DC-PGT is used to clear prostaglandins (PGs) and other metabolically active organic anions from the body (in the liver, fetal liver, lung and placenta) it is easy to suppose that an alteration in the capacity of this mechanism could augment the allergic response. Prostaglandin $PGF_{2\alpha}$ and PGD_2, and PGG_2 and thrombaxane A_2 can cause airway obstruction, particularly in the peripheral lung, while PGE_2 and PGI_2 are bronchodilators. Use of the transporter of the invention could help transport or remove these prostaglandins to modulate airway obstruction.

Additionally, prostaglandins play an important role in secondary immunosuppression seen following surgical stress. Alexander (1990) J. Trauma 30:S70; Faist, et al. (1987) J. Trauma 27:837; Ninneman, et al. (1984) J. Trauma 24:201; Wood, et al. (1987) Arch. Surg. 122:179; Polk, et al. in Eremin and Sewell (eds. 1992) The Immunological Basis of Surgical Science and Practice, Oxford U. Press. In particular, PGE2 inhibits lymphocyte proliferation, decreases IL-2 release, decreases response to IL-2, inhibits natural killer cells, and activates supressor cells. Major injury has been shown to result in increased production of PGE2 from inhibitory macrophages, with a resulting decrease in production of IL-1 and IL-2. This effect may persist for 7 to 10 days after major injury. Other studies have shown no increase in circulating PGE2 following burns but did find increased local production with increased sensitivity of lymphocytes to the action of PGE2.

Prostaglandin E2, through locally produced vasodilatory effects, may play a role in rheumatoid arthritis by promoting the entry of inflammatory cells into the joint. Once in the synovial fluid, polymorphonuclear leukocytes can ingest immune complexes, which, in turn, cause neutrophils to produce reactive oxygen

metabolites and other inflammatory mediators to further enchance an inflammatory cascade. Henson, et al. (1987) J. Clin. Invest. 79:699.

Accordingly, it is possible to use the present invention to modulate prostaglandins in a subject suffering from trauma, injury, disease or in post-surgical treatments.

Immune system cells may be synthesizing PGs and thus using DC-PGT in an efflux role for removing PGs from the intracellular space may be useful. Equally, DC-PGT might transport a specific organic anion. Abnormal proliferation, regeneration, degeneration, and atrophy may be modulated by appropriate therapeutic treatment using the compositions provided herein. For example, a disease or disorder associated with abnormal function of a prostaglandin transporter should be a likely target for a substrate or blocking substrate. Alternatively, the transporter may be a useful means for supplying important metabolites or metabolite blockers to the respective cells.

For example, transformation with the transporter may increase availability of the substrate to the cell. In certain situations, a prostaglandin analog might be advantageously supplied to the cell. The prostaglandin analog might confer high susceptibility to further treatment, e.g., radiation sensitivity or otherwise, or may directly affect normal metabolism, e.g., nucleic acid related enzymes. Alternatively, the transporter may be useful to screen for antagonists or inhibitors, which might be effective in blocking the normal availability to the cell of the natural substrate. Screening methods for such prostaglandin analogs are provided.

Screening using prostaglandin transporter for binding metabolites or compounds having binding affinity to the transporter can be performed, including isolation of associated components. Subsequent biological assays can then be utilized to determine if the compound has intrinsic biological activity and is therefore an agonist or antagonist in that it blocks an activity of the transporter. In particular, prostaglandin analogs may be useful in blocking binding of the natural target or otherwise blocking transporter activity. Alternatively, various other

analogs may be useful in blocking an ion transporter, or organic anion source. This invention further contemplates the therapeutic use of antibodies to prostaglandin transporter as antagonists. This approach should be particularly useful with other prostaglandin transporter species variants and other members of the family.

Antagonists of the transporter activity, e.g., antibodies which block the transport, may be useful in various medical conditions. These would include immune, inflammatory or allergic abnormalities, all of which are important where transfer of organic anions take place. Certain congenital diseases of prostaglandin physiology will be susceptible to such a therapeutic approach.

The HDTEA84, HSLJD37R, RANKL, HCC5, MD-1, or MD-2 (naturally occurring or recombinant), fragments thereof, and antibodies thereto, along with compounds identified as having binding affinity to them, should be useful in the treatment of conditions associated with abnormal physiology or development, including abnormal proliferation, e.g., cancerous conditions, or degenerative conditions. In particular, modulation of development of lymphoid cells will be achieved by appropriate therapeutic treatment using the compositions provided herein. For example, a disease or disorder associated with abnormal expression or abnormal signaling by a ligand or receptor should be a likely target for an agonist or antagonist of the antigen. The antigen plays a role in regulation or development of hematopoietic cells, e.g., lymphoid cells, which affect immunological responses, e.g., autoimmune disorders.

In particular, the antigen may provide a costimulatory signal to cell activation, or be involved in regulation of cell proliferation or differentiation. Thus, the HDTEA84, HSLJD37R, RANKL, HCC5, MD-1, or MD-2 will likely modulate cells which possess a receptor therefor, e.g., T cell mediated interactions with other cell types. These interactions would lead, in particular contexts, to modulation of cell growth, cytokine synthesis by those or other cells, or development of particular effector cells.

Moreover, the HDTEA84, HSLJD37R, RANKL, HCC5, MD-1, or MD-2 or antagonists could redirect T cell responses, e.g., between Th1 and Th2 polarization, or with Th0 cells, or may affect B cells or other lymphoid cell subsets. Among these agonists should be various antibodies which recognize the appropriate epitopes, e.g., which mimic binding of ligand or receptor to its partner. Alternatively, they may bind to epitopes which sterically can block receptor binding. Bone morphogenesis may be regulated by these receptor segments.

The ligands or receptors may provide a selective and powerful way to modulate immune responses in abnormal situations, e.g., autoimmune disorders, including rheumatoid arthritis, systemic lupus erythematosis (SLE), Hashimoto's autoimmune thyroiditis, as well as acute and chronic inflammatory responses in which T cell activation, expansion, and/or immunological T cell memory play an important role. See also Samter, et al. (eds) Immunological Diseases vols. 1 and 2, Little, Brown and Co. Regulation of bone morphogenesis, T cell activation, expansion, and/or cytokine release by the naturally occurring secreted form of HDTEA84, HSLJD37R, RANKL, HCC5, MD-1, or MD-2, or an antagonist thereof, may be effected.

In addition, certain combination compositions with other modulators of signaling would be useful, especially with the TNF receptor-like genes. Such other signaling molecules might include, e.g., TCR reagents, CD40, CD40L, CTLA-8, CD28, SLAM, FAS, osteoprotegerin, and their respective antagonists, including antibodies.

Cyclin E2 nucleotides, e.g., human cyclin E2 DNA or RNA, may be used as a component in a forensic assay. For instance, the nucleotide sequences provided may be labeled using, e.g., ^{32}P or biotin and used to probe standard restriction fragment polymorphism blots, providing a measurable character to aid in distinguishing between individuals. Such probes may be used in well-known forensic techniques such as genetic fingerprinting. In addition, nucleotide probes made from cyclin E2 sequences may be used in in situ assays to detect chromosomal abnormalities. For instance, rearrangements in the human chromosome encoding a cyclin

E2 gene may be detected via well-known in situ techniques, using cyclin E2 probes in conjunction with other known chromosome markers. The cyclin E2 gene may have useful prognostic utility in various cancers, e.g., breast, etc.

Antibodies and other binding agents directed towards cyclin E2 proteins or nucleic acids may be used to purify the corresponding cyclin E2 molecule. As described in the Examples below, antibody purification of cyclin E2 protein components is both possible and practicable. Antibodies and other binding agents may also be used in a diagnostic fashion to determine whether cyclin E2 protein components are present in a tissue sample or cell population using well-known techniques described herein. The ability to attach a binding agent to a cyclin E2 protein provides a means to diagnose disorders associated with cyclin E2 protein misregulation. Antibodies and other cyclin E2 protein binding agents may also be useful as histological markers. As described in the examples below, cyclin E2 protein expression is limited to specific tissue types. By directing a probe, such as an antibody or nucleic acid to a cyclin E2 protein it is possible to use the probe to distinguish tissue and cell types in situ or in vitro.

This invention also provides reagents with significant therapeutic value. The cyclin E2 protein (naturally occurring or recombinant), fragments thereof, and antibodies thereto, along with compounds identified as having binding affinity to a cyclin E2 protein, can be useful in the treatment of conditions associated with abnormal physiology or development, including abnormal proliferation, e.g., cancerous conditions, or degenerative conditions. Abnormal proliferation, regeneration, degeneration, and atrophy may be modulated by appropriate therapeutic treatment using the compositions provided herein. For example, a disease or disorder associated with abnormal expression or abnormal signaling by a cyclin E2 protein is a target for an agonist or antagonist of the protein. The proteins likely play a role in regulation or development of neuronal or hematopoietic cells, e.g., lymphoid cells, which affect immunological responses.

Various abnormal conditions are known in each of the cell types shown to possess, e.g., HDTEA84, mRNA by Northern blot analysis. See Berkow (ed.) The Merck Manual of Diagnosis and Therapy, Merck & Co., Rahway, NJ; Thorn, et al. Harrison's Principles of Internal Medicine, McGraw-Hill, NY; and Weatherall, et al. (eds.) Oxford Textbook of Medicine, Oxford University Press, Oxford. Many other medical conditions and diseases involve T cells or are T cell mediated, and many of these may be responsive to treatment by an agonist or antagonist provided herein. See, e.g., Stites and Terr (eds; 1991) Basic and Clinical Immunology Appleton and Lange, Norwalk, CT; and Samter, et al. (eds) Immunological Diseases Little, Brown and Co. These problems should be susceptible to prevention or treatment using compositions provided herein.

Specific, or selective, antibodies can be purified and then administered to a patient, veterinary or human. These reagents can be combined for therapeutic use with additional active or inert ingredients, e.g., in conventional pharmaceutically acceptable carriers or diluents, e.g., immunogenic adjuvants, along with physiologically innocuous stabilizers, excipients, or preservatives. These combinations can be sterile filtered and placed into dosage forms as by lyophilization in dosage vials or storage in stabilized aqueous preparations. This invention also contemplates use of antibodies or binding fragments thereof, including forms which are not complement binding.

Drug screening using proteins or fragments thereof can be performed to identify compounds having binding affinity to or other relevant biological effects on antigen functions, including isolation of associated components. Subsequent biological assays can then be utilized to determine if the compound has intrinsic stimulating activity or is a blocker or antagonist in that it blocks the activity of the antigen, e.g., mutein antagonists. Likewise, a compound having intrinsic stimulating activity can activate the signal pathway and is thus an agonist in that it overcomes any blocking activity of these soluble forms of receptors. This invention further contemplates the therapeutic use of blocking antibodies to ligands or receptors as agonists or

antagonists and of stimulatory molecules, e.g., muteins, as agonists. This approach should be particularly useful with other soluble receptor species variants.

Another therapeutic approach included within the invention involves direct administration of reagents or compositions by any conventional administration techniques (e.g., but not restricted to local injection, inhalation, or administered systemically), to the subject with an immune, allergic, or trauma disorder. The reagents, formulations, or compositions included within the bounds and metes of the invention may also be targeted to specific cells or transporters by methods described herein. The actual dosage of reagent, formulation, or composition that modulates an immune, allergic, or trauma disorder depends on many factors, including the size and health of an organism, however one of ordinary skill in the art can use the following teachings describing the methods and techniques for determining clinical dosages. See, e.g., Spilker (1984) Guide to Clinical Studies and Developing Protocols, Raven Press Books, Ltd., New York, pp. 7-13, 54-60; Spilker (1991) Guide to Clinical Trials, Raven Press, Ltd., New York, pp. 93-101; Craig and Stitzel (eds. 1986) Modern Pharmacology, 2d ed., Little, Brown and Co., Boston, pp. 127-33; Speight (ed. 1987) Avery's Drug Treatment: Principles and Practice of Clinical Pharmacology and Therapeutics, 3d ed., Williams and Wilkins, Baltimore, pp. 50-56; Tallarida, et al. (1988) Principles in General Pharmacology, Springer-Verlag, New York, pp. 18-20). Generally, the dose will be in the range of about between 0.5 fg/ml and 500 µg/ml, inclusive, final concentration administered per day to an adult in a pharmaceutically acceptable carrier.

The quantities of reagents necessary for effective therapy will depend upon many different factors, including means of administration, target site, physiological state of the patient, and other medicants administered. Thus, treatment dosages should be titrated to optimize safety and efficacy. Typically, dosages used in vitro may provide useful guidance in the amounts useful for in situ administration of these reagents. Animal testing of effective doses for treatment of particular disorders will provide

further predictive indication of human dosage. Various considerations are described, e.g., in Gilman, et al. (eds. 1990) Goodman and Gilman's: The Pharmacological Bases of Therapeutics, 8th Ed., Pergamon Press; and Remington's Pharmaceutical Sciences, 17th ed. (1990), Mack Publishing Co., Easton, Penn. Methods for administration are discussed, e.g., for oral, intravenous, intraperitoneal, or intramuscular administration, transdermal diffusion, and others. Pharmaceutically acceptable carriers will include water, saline, buffers, and other compounds described, e.g., in the Merck Index, Merck & Co., Rahway, New Jersey. Dosage ranges would ordinarily be expected to be in amounts lower than 1 mM concentrations, typically less than about 10 μM concentrations, usually less than about 100 nM, preferably less than about 10 pM (picomolar), and most preferably less than about 1 fM (femtomolar), with an appropriate carrier. Slow release formulations, or a slow release apparatus will often be utilized for continuous or long term administration. See, e.g., Langer (1990) Science 249:1527-1533.

Ligands, receptors, enzymes, fragments thereof, and antibodies to it or its fragments, antagonists, and agonists, may be administered directly to the host to be treated or, depending on the size of the compounds, it may be desirable to conjugate them to carrier proteins such as ovalbumin or serum albumin prior to their administration. Therapeutic formulations may be administered in many conventional dosage formulations. While it is possible for the active ingredient to be administered alone, it is preferable to present it as a pharmaceutical formulation. Formulations typically comprise at least one active ingredient, as defined above, together with one or more acceptable carriers thereof. Each carrier should be both pharmaceutically and physiologically acceptable in the sense of being compatible with the other ingredients and not injurious to the patient. Formulations include those suitable for oral, rectal, nasal, topical, or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by methods well known in the art of pharmacy. See, e.g., Gilman,

et al. (eds. 1990) Goodman and Gilman's: The Pharmacological Bases of Therapeutics, 8th Ed., Pergamon Press; and Remington's Pharmaceutical Sciences, 17th ed. (1990), Mack Publishing Co., Easton, Penn.; Avis, et al. (eds. 1993) Pharmaceutical Dosage Forms: Parenteral Medications, Dekker, New York; Lieberman, et al. (eds. 1990) Pharmaceutical Dosage Forms: Tablets, Dekker, New York; and Lieberman, et al. (eds. 1990) Pharmaceutical Dosage Forms: Disperse Systems, Dekker, New York. The therapy of this invention may be combined with or used in association with other agents, e.g., other modulators of cell activation, e.g., CD40, CD40 ligand, CD28, CTLA-4, B7, B70, SLAM, T cell receptor signaling entities, or their respective antagonists.

Both the naturally occurring and the recombinant forms of the proteins of this invention are particularly useful in kits and assay methods which are capable of screening compounds for binding activity to the proteins. Several methods of automating assays have been developed in recent years so as to permit screening of tens of thousands of compounds in a short period. See, e.g., Fodor, et al. (1991) Science 251:767-773, which describes means for testing of binding affinity by a plurality of defined polymers synthesized on a solid substrate. The development of suitable assays can be greatly facilitated by the availability of large amounts of purified, soluble proteins or nucleic acids as provided by this invention.

Other methods can be used to determine the critical residues in the substrate, ligand, or receptor binding interactions. Mutational analysis can be performed, e.g., see Somoza, et al. (1993) J. Exp. Med. 178:549-558, to determine specific residues critical in the interaction and/or signaling. This will allow study of both extracellular domains, involved in the soluble ligand interaction, or intracellular domain of a transmembrane form, which provides interactions important in intracellular signaling.

For example, antagonists can normally be found once the antigen has been structurally defined, e.g., by tertiary structure data. Testing of potential interacting analogs is now possible

upon the development of highly automated assay methods using a purified protein. In particular, new agonists and antagonists will be discovered by using screening techniques described herein. Of particular importance are compounds found to have a combined binding affinity for a spectrum of protein molecules, e.g., compounds which can serve as antagonists for species variants of the antigens.

One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant DNA molecules expressing desired protein. Cells may be isolated which express a selected protein in isolation from other molecules. Such cells, either in viable or fixed form, can be used for standard binding partner binding assays. See also, Parce, et al. (1989) Science 246:243-247; and Owicki, et al. (1990) Proc. Nat'l Acad. Sci. USA 87:4007-4011, which describe sensitive methods to detect cellular responses.

Another technique for drug screening involves an approach which provides high throughput screening for compounds having suitable binding affinity to a desired target protein, and is described in detail in Geysen, European Patent Application 84/03564, published on September 13, 1984. First, large numbers of different small peptide test compounds are synthesized on a solid substrate, e.g., plastic pins or some other appropriate surface, see Fodor, et al. (1991). Then the pins are reacted with solubilized, unpurified or solubilized, purified target protein, and washed. The next step involves detecting bound protein.

Rational drug design may also be based upon structural studies of the molecular shapes of the protein and other effectors or analogs. Effectors may be other proteins which mediate other functions in response to binding, or other proteins which normally interact. One means for determining which sites interact with specific other proteins is a physical structure determination, e.g., x-ray crystallography or 2 dimensional NMR techniques. These will provide guidance as to which amino acid residues form molecular contact regions. For a detailed description of protein structural determination, see, e.g., Blundell and Johnson (1976) Protein Crystallography, Academic Press, New York.

IX. Kits

This invention also contemplates use of the proteins, fragments thereof, peptides, and their fusion products in a variety of diagnostic kits and methods for detecting, e.g., the presence of protein or binding partner. Typically the kit will have a compartment containing either a described polypeptide or gene segment or a reagent which recognizes one or the other, e.g., fragments or antibodies. Alternatively, kits may be nucleic acid based.

A kit for determining the binding affinity of a test compound to, e.g., an HDTEA84, would typically comprise a test compound; a labeled compound, for example a binding partner or antibody having known binding affinity for HDTEA84; a source of HDTEA84 (naturally occurring or recombinant); and a means for separating bound from free labeled compound, such as a solid phase for immobilizing the molecule. Once compounds are screened, those having suitable binding affinity to the antigen can be evaluated in suitable biological assays, as are well known in the art, to determine whether they act as agonists or antagonists to the HDTEA84 signaling pathway. The availability of recombinant HDTEA84 polypeptides also provide well defined standards for calibrating such assays.

A preferred kit for determining the concentration of, e.g., an HDTEA84 in a sample would typically comprise a labeled compound, e.g., binding partner or antibody, having known binding affinity for the antigen, a source of antigen (naturally occurring or recombinant) and a means for separating the bound from free labeled compound, e.g., a solid phase for immobilizing the HDTEA84. Compartments containing reagents, and instructions, will normally be provided.

Antibodies, including antigen binding fragments, specific for, e.g., the HDTEA84 or fragments, are useful in diagnostic applications to detect the presence of elevated levels of HDTEA84 and/or its fragments. Such diagnostic assays can employ lysates, live cells, fixed cells, immunofluorescence, cell cultures, body fluids, and further can involve the detection of antigens related

to the antigen in serum, or the like. Diagnostic assays may be homogeneous (without a separation step between free reagent and antigen-binding partner complex) or heterogeneous (with a separation step). Various commercial assays exist, such as radioimmunoassay (RIA), enzyme-linked immunosorbent assay (ELISA), enzyme immunoassay (EIA), enzyme-multiplied immunoassay technique (EMIT), substrate-labeled fluorescent immunoassay (SLFIA), and the like. See, e.g., Van Vunakis, et al. (1980) Meth Enzymol. 70:1-525; Harlow and Lane (1980) Antibodies: A Laboratory Manual, CSH Press, NY; and Coligan, et al. (eds. 1993) Current Protocols in Immunology, Greene and Wiley, NY.

Anti-idiotypic antibodies may have similar use to diagnose presence of antibodies against a described protein, as such may be diagnostic of various abnormal states. Overproduction of prostaglandin transporter may reflect various medical conditions, which may be diagnostic of abnormal physiological states, particularly in proliferative cell conditions such as cancer or abnormal differentiation. For example, leukemias and lymphomas may exhibit altered transporter expression, which may reflect their altered physiology and may provide means to selectively target. Alternatively, overproduction of HDTEA84, HSLJD37R, RANKL, HCC5, MD-1, or MD-2 may result in production of various immunological reactions which may be diagnostic of abnormal physiological states, particularly in proliferative cell conditions such as cancer or abnormal activation or differentiation. Expression levels of DC-PGT, Dubs, or cyclin E2 may likewise be diagnostic of specific therapeutic conditions, advantageous or disadvantageous.

Frequently, the reagents for diagnostic assays are supplied in kits, so as to optimize the sensitivity of the assay. For the subject invention, depending upon the nature of the assay, the protocol, and the label, either labeled or unlabeled antibody or binding partner, or labeled HDTEA84 is provided. This is usually in conjunction with other additives, such as buffers, stabilizers, materials necessary for signal production such as substrates for enzymes, and the like. Preferably, the kit will also contain instructions for proper use and disposal of the contents after

use. Typically the kit has compartments for each useful reagent. Desirably, the reagents are provided as a dry lyophilized powder, where the reagents may be reconstituted in an aqueous medium providing appropriate concentrations of reagents for performing the assay.

Many of the aforementioned constituents of the drug screening and the diagnostic assays may be used without modification or may be modified in a variety of ways. For example, labeling may be achieved by covalently or non-covalently joining a moiety which directly or indirectly provides a detectable signal. In these assays, the binding partner, test compound, HDTEA84, or antibodies thereto can be labeled either directly or indirectly. Possibilities for direct labeling include label groups: radiolabels such as ^{125}I, enzymes (U.S. Pat. No. 3,645,090) such as peroxidase and alkaline phosphatase, and fluorescent labels (U.S. Pat. No. 3,940,475) capable of monitoring the change in fluorescence intensity, wavelength shift, or fluorescence polarization. Possibilities for indirect labeling include biotinylation of one constituent followed by binding to avidin coupled to one of the above label groups.

There are also numerous methods of separating the bound from the free polypeptide, or alternatively the bound from the free test compound. The polypeptide can be immobilized on various matrixes followed by washing. Suitable matrices include plastic such as an ELISA plate, filters, and beads. See, e.g., Coligan, et al. (eds. 1993) Current Protocols in Immunology, Vol. 1, Chapter 2, Greene and Wiley, NY. Other suitable separation techniques include, without limitation, the fluorescein antibody magnetizable particle method described in Rattle, et al. (1984) Clin. Chem. 30:1457-1461, and the double antibody magnetic particle separation as described in U.S. Pat. No. 4,659,678.

Methods for linking proteins or their fragments to the various labels have been extensively reported in the literature and do not require detailed discussion here. Many of the techniques involve the use of activated carboxyl groups either through the use of carbodiimide or active esters to form peptide bonds, the formation of thioethers by reaction of a mercapto group

with an activated halogen such as chloroacetyl, or an activated olefin such as maleimide, for linkage, or the like. Fusion proteins will also find use in these applications.

Another diagnostic aspect of this invention involves use of oligonucleotide or polynucleotide sequences taken from the sequence of a described protein. These sequences can be used as probes for detecting levels of the message in samples from patients suspected of having an abnormal condition, e.g., cancer or developmental problem. Since the antigen is a marker for activation, it may be useful to determine the numbers of activated T cells to determine, e.g., when additional suppression may be called for. The preparation of both RNA and DNA nucleotide sequences, the labeling of the sequences, and the preferred size of the sequences has received ample description and discussion in the literature. See, e.g., Langer-Safer, et al. (1982) Proc. Nat'l. Acad. Sci. 79:4381-4385; Caskey (1987) Science 236:962-967; and Wilchek, et al. (1988) Anal. Biochem. 171:1-32.

Alternatively, antibodies may be employed which can recognize specific duplexes, including DNA duplexes, RNA duplexes, DNA-RNA hybrid duplexes, or DNA-protein duplexes. The antibodies in turn may be labeled and the assay carried out where the duplex is bound to a surface, so that upon the formation of duplex on the surface, the presence of antibody bound to the duplex can be detected. The use of probes to the novel anti-sense RNA may be carried out in any conventional techniques such as nucleic acid hybridization, plus and minus screening, recombinational probing, hybrid released translation (HRT), and hybrid arrested translation (HART). This also includes amplification techniques such as polymerase chain reaction (PCR).

Diagnostic kits which also test for the qualitative or quantitative presence of other markers are also contemplated. Diagnosis or prognosis may depend on the combination of multiple indications used as markers. Thus, kits may test for combinations of markers. See, e.g., Viallet, et al. (1989) Progress in Growth Factor Res. 1:89-97. Other kits may be used to evaluate T cell subsets.

X. Methods for Isolating Substrates/Specific Partners

The DC-PGT should interact with its substrate target. The substrate will be similar to the organic molecules which are subject to transport. The Dubs and cyclin E2 will also be screened for substrate identification.

The HDTEA84, HSLJD37R, and RANKL protein should interact with a TNF ligand, based, e.g., upon its similarity in structure and function to other cell surface antigens exhibiting similar structure and cell type specificity of expression. The MD-1 and MD-2 antigens are related to known proteins, which interact with B cell antigens. Methods to isolate a ligand are made available by the ability to make purified protein for screening programs. Similar techniques will be applicable to the HCC5 chemokine, and the MD-1 and MD-2 surface receptors.

Sequences provided herein will allow for screening or isolation of specific ligands. Many methods exist for expression cloning, panning, affinity isolation, or other means to identify a ligand. A two-hybrid selection system may also be applied making appropriate constructs with the available sequences, as appropriate. See, e.g., Fields and Song (1989) Nature 340:245-246.

The broad scope of this invention is best understood with reference to the following examples, which are not intended to limit the invention to specific embodiments.

EXAMPLES

General Methods

Some of the standard methods are described or referenced, e.g., in Maniatis, et al. (1982) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory, Cold Spring Harbor Press; Sambrook, et al. (1989) Molecular Cloning: A Laboratory Manual (2d ed.), vols. 1-3, CSH Press, NY; Ausubel, et al., Biology, Greene Publishing Associates, Brooklyn, NY; or Ausubel, et al. (1987 and Supplements) Current Protocols in Molecular Biology, Greene and Wiley, New York; Innis, et al. (eds. 1990) PCR Protocols: A Guide to Methods and Applications, Academic Press, N.Y. Methods for protein purification include such methods as ammonium sulfate precipitation, column chromatography, electrophoresis, centrifugation, crystallization, and others. See, e.g., Ausubel, et al. (1987 and periodic supplements); Deutscher (1990) "Guide to Protein Purification" in Methods in Enzymol. vol. 182, and other volumes in this series; and manufacturer's literature on use of protein purification products, e.g., Pharmacia, Piscataway, N.J., or Bio-Rad, Richmond, CA. Combination with recombinant techniques allow fusion to appropriate segments, e.g., to a FLAG sequence or an equivalent which can be fused via a protease-removable sequence. See, e.g., Hochuli (1990) "Purification of Recombinant Proteins with Metal Chelate Absorbent" in Setlow (ed.) Genetic Engineering, Principle and Methods 12:87-98, Plenum Press, N.Y.; and Crowe, et al. (1992) QIAexpress: The High Level Expression & Protein Purification System QIAGEN, Inc., Chatsworth, CA. Cell culture techniques are described in Doyle, et al. (eds. 1994) Cell and Tissue Culture: Laboratory Procedures, John Wiley and Sons, NY.

Standard immunological techniques are described, e.g., in Hertzenberg, et al. (eds. 1996) Weir's Handbook of Experimental Immunology vols. 1-4, Blackwell Science; Coligan (1991) Current Protocols in Immunology Wiley/Greene, NY; and Methods in Enzymology volumes. 70, 73, 74, 84, 92, 93, 108, 116, 121, 132, 150, 162, and 163.

FACS analyses are described in Melamed, et al. (1990) Flow Cytometry and Sorting Wiley-Liss, Inc., New York, NY; Shapiro (1988) Practical Flow Cytometry Liss, New York, NY; and Robinson, et al. (1993) Handbook of Flow Cytometry Methods Wiley-Liss, New York, NY. Fluorescent labeling of appropriate reagents was performed by standard methods.

The FASTA (Pearson and Lipman, 1988) and BLAST (Altschul, et al. (1990) J. Mol. Biol. 215:403-410) programs were used to comb nonredundant protein and nucleotide databases (Benson, et al. (1994) Nucl. Acids Res. 22:3441-3444; Bairoch and Boeckmann (1994) Nucl. Acids Res. 22:3578-3580) with the resultant cDNA and encoded protein sequences. The sensitive search strategies of Altschul, et al. (1994) Nature Genet. 6:119-129; and Koonin, et al. (1994) EMBO J. 13:493-503; served as examples of how to locate distant structural homologues of protein chains. Multiple alignments of collected homologues were carried out with ClustalW (Thompson, et al. (1994) Comp. Applic. Biosci. 10:19-29) and MACAW (Schuler, et al. (1991) Proteins 9:180-190).

The membrane topologies of proteins, e.g., DC-PGT, and a cohort of putative homologues were analyzed by a variety of methods that sought to determine the consensus number of domains, e.g., hydrophobic membrane-spanning helices and the likely cytoplasmic or extracellular exposure of the hydrophilic connecting loops. For single sequence analysis, the ALOM and MTOP (Klein, et al. (1985) Biochim. Biophys. Acta 815:468-476; and Hartmann, et al. (1989) Proc. Natl. Acad. Sci. USA 86:5786-5790) programs were accessed from the PSORT World-Wide Web site (Nakai and Kanehisa (1991) Proteins 11:95-110; and Nakai and Kanehisa (1992) Genomics 14:897-911); in turn, the TopPredII program (Claros and von Heijne (1994) Comp. Applic. Biosci. 10:685-686; MacIntosh PPC version) was used to parse chains into probable hydrophobic transmembrane and loop regions of DC-PGT, and further predict the localization of these latter regions by prevalence of charged residue types (von Heijne (1992) J. Mol. Biol. 225:487-494; and Sippos and von Heijne (1993) Eur. J. Biochem. 213:1333-

1340). MEMSAT (Jones, et al. (1994) Biochem. 33:3038-3049; MS-DOS PC version) was likewise used to fit individual sequences into statistically-based topology models that render judgment on membrane spanning and loop chain segments. Two Web-accessible programs that are able to make use of evolutionary data by analyzing multiply aligned sequences are PHD (Rost, et al. (1994) Comp. Applic. Biosci. 10:53-60; and Rost, et al. (1995) Protein Sci. 4:521-533) and TMAP (Persson and Argos (1994) J. Mol. Biol. 237:182-192); the former utilizes a neural network system to accurately predict the shared location of helical transmembrane segments in a protein family. Similar analysis of other proteins can be performed.

I. Generation of Dendritic Cells

Human CD34+ cells are obtained as follows. See, e.g., Caux, et al. (1995) pages 1-5 in Banchereau and Schmitt Dendritic Cells in Fundamental and Clinical Immunology Plenum Press, NY. Peripheral or cord blood cells, sometimes CD34+ selected, are cultured in the presence of Stem Cell Factor (SCF), GM-CSF, and TNF-α in endotoxin free RPMI 1640 medium (GIBCO, Grand Island, NY) supplemented with 10% (v/v) heat-inactivated fetal bovine serum (FBS; Flow Laboratories, Irvine, CA), 10 mM HEPES, 2 mM L-glutamine, 5 X 10^{-5} M 2-mercaptoethanol, penicillin (100 µg/ml). This is referred to as complete medium.

CD34+ cells are seeded for expansion in 25 to 75 cm^2 flasks (Corning, NY) at 2 x 10^4 cells/ml. Optimal conditions are maintained by splitting these cultures at day 5 and 10 with medium containing fresh GM-CSF and TNF-α (cell concentration: 1-3 x 10^5 cells/ml). In certain cases, cells are FACS sorted for CD1a expression at about day 6.

In certain situations, cells are routinely collected after 12 days of culture, eventually adherent cells are recovered using a 5 mM EDTA solution. In other situations, the CD1a+ cells are activated by resuspension in complete medium at 5 x 10^6 cells/ml and activated for the appropriate time (e.g., 1 or 6 h) with 1

µg/ml phorbol 12-myristate 13-acetate (PMA, Sigma) and 100 ng/ml ionomycin (Calbiochem, La Jolla, CA). These cells are expanded for another 6 days, and RNA isolated for cDNA library preparation. Other specific cell types may be similarly isolated.

II. RNA Isolation and Library Construction

Total RNA is isolated using, e.g., the guanidine thiocyanate/CsCl gradient procedure as described by Chirgwin, et al. (1978) Biochem. 18:5294-5299.

Alternatively, poly(A)+ RNA is isolated using the OLIGOTEX mRNA isolation kit (QIAGEN). Double stranded cDNA are generated using, e.g., the SUPERSCRIPT plasmid system (Gibco BRL, Gaithersburg, MD) for cDNA synthesis and plasmid cloning. The resulting double stranded cDNA is unidirectionally cloned, e.g., into pSport1 and transfected by electroporation into ELECTROMAX DH10BTM Cells (Gibco BRL, Gaithersburg, MD).

III. Sequencing

DNA isolated from randomly picked clones, or after subtractive hybridization using inactivated cells, are subjected to nucleotide sequence analysis using standard techniques. Alternatively, selected isolated clones can be selected. A Taq DiDeoxy Terminator cycle sequencing kit (Applied Biosystems, Foster City, CA) can be used. The labeled DNA fragments are separated using a DNA sequencing gel of an appropriate automated sequencer. Alternatively, the isolated clone is sequenced as described, e.g., in Maniatis, et al. (Current ed.) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory, Cold Spring Harbor Press; Sambrook, et al. (Current ed.) Molecular Cloning: A Laboratory Manual, (2d ed.), vols. 1-3, CSH Press, NY; Ausubel, et al., Biology, Greene Publishing Associates, Brooklyn, NY; or Ausubel, et al. (Current ed., and Supplements) Current Protocols in Molecular Biology, Greene/Wiley, New York. Chemical sequencing methods are also available, e.g., using Maxim and Gilbert sequencing techniques.

IV. Recombinant gene constructs

Poly(A)$^+$ RNA is isolated from appropriate cell populations, e.g., using the FastTrack mRNA kit (Invitrogen, San Diego, CA). Samples are electrophoresed, e.g., in a 1% agarose gel containing formaldehyde and transferred to a GeneScreen membrane (NEN Research Products, Boston, MA). Hybridization is performed, e.g., at 65° C in 0.5 M $NaHPO_4$ pH 7.2, 7% SDS, 1 mM EDTA, and 1% BSA (fraction V) with ^{32}P-dCTP labeled DC gene cDNA at 10^7 cpm/ml. After hybridization, filters are washed three times at 50° C in 0.2X SSC, 0.1% SDS, e.g., for 30 min, and exposed to film for 24 h. A positive signal will typically be 2X over background, preferably 5-25X.

The recombinant gene construct may be used to generate a probe for detecting the message. The insert may be excised and used in the detection methods described above. Various standard methods for cross species hybridization and washes are well known in the art. See, e.g., Sambrook, et al. and Ausubel.

V: Gene Cloning

The HDTEA84 was assembled by careful analysis of ESTs found in various databases. These ESTs were from cDNA libraries derived from Hodgkin's lymphoma, endothelial cells, keratinocytes, prostate, and cerebellum. PCR primers are designed and synthesized and a PCR product is obtained from any of these libraries. This product is used as a hybridization clone to screen these libraries for a full length clone, which may include a transmembrane segment.

Likewise, the HSLJD37R was identified from sequences derived from cDNA libraries from: smooth muscle, pancreas tumor, adipocytes, HUVEC cells, adult pulmonary, endothelial cells, prostate cell line PC3, microvascular endothelial cells, fetal heart, and dendritic cells. A GenBank report by Pan, et al. has been submitted. See GenBank Accession 3549263. Other sequences were detected in libraries from: multiple sclerosis lesions, breast, kidney, and germinal center B cells. RT-PCT showed signal in B cells, PBL, granulocytes, T cells, monocytes, dendritic cell subpopulations including PMA/ionomycin treated, U937 cells, JY

cells, MRC5 cells, CHA, Jurkat, and YC1 cells. This suggests that the transcript is widely expressed.

RANKL was also identified in cDNA libraries from specific tissues, as described. Likewise, the HCC5 chemokine sequence was identified. The Dub11 and Dub12 genes were identified, in part, from their similarity to known Dub1 and Dub2 genes. The MD-1 and MD-2 were identified, in part, from their similarity to the ligand for the RP105 gene. The cyclin E2 was identified based upon its similarity to cyclin E.

VI. Expression Profile

To examine DC-PGT mRNA expression standard Northern Blot Analysis using a RT-PCR fragment of DC-PGT were carried out against human tissue, e.g., Northern blots containing approximately 10 to 20 µg of total RNA are run in formaldehyde gels and transferred to Nytran membranes (Schleicher & Schuell, Keene, NH) by standard methods, and blots were hybridized with a labeled PCR fragment of DC-PGT and washed at 65° C. cDNA can be isolated from cells, embryonic tissues, and adult organs using RNAzol solution (Tel-test, Inc., Friendswood, TX) according to manufacturer's instructions. Large amounts of plasmid DNA containing differential display PCR products are prepared using the QIAGEN Plasmid Maxi Kit (QIAGEN) following the manufacturer's instructions. Plasmid DNA is cut with EcoRI (Boehringer Mannheim) or BstXI (NE Biolabs, Mass.), gel extracted with the QIAEX gel extraction kit (QIAGEN) and random primed with [^{32}P]dCTP (Amersham) using the Prime-It II kit (Stratagene, La Jolla, CA), all in accordance with manufacturer's instructions. Various primers may be used to quantitate expression of message. Means to block DNA hybridization signal, or RNA isolation, will be applicable to quantitate roughly the amount of expression of appropriate RNAs.

The results revealed mRNA of one band at approximately 9.0 kB, another band at approximately 3.0 kB, and a 4.4 kB size which is consistent with the size predicted for the SEQ ID NO: 1 nucleic acid. The smaller mRNA product band could be an alternatively spliced form of SEQ ID NO: 1. DC-PGT is highly expressed in both

activated and non-activated dendritic cells (DC), activated monocytes, activated granulocytes and adult lung. No expression was found in T or PBL cells (either activated or non-activated). Minor expression was detected in B cell (both activated and non-activated) and limited expression was detected in the brain. The results of the northern analysis suggests an expression in macrophages, rather than monocytes (Kuppfer cells in the liver, microglial cells in the brain, alveolar macrophages in the lung) particularly as there is no expression in PBL. Southern expression analysis carried out using common techniques confirmed the expression pattern revealed in the Northern analysis.

For example, the DC-PGT tissue distribution seems to have highest mRNA levels in kidney, placenta, liver, bone marrow, thymus, spleen, lung, and some in testis. This distribution corresponds to organs with especially important ion exchange features, e.g., Na, K, or Ca, or in hematopoietic organs. Generally, the expression is higher in fibroblast and hematopoietic cells compared to neuronal cells.

A probe specific for cDNA encoding the HDTEA84, HSLJD37R, or RANKL is used to determine tissue distribution of message encoding the antigen. Standard hybridization probes may be used to do a Northern analysis of RNA from appropriate sources, either cells, e.g., stimulated, or in various physiological states, in various tissues, e.g., spleen, liver, thymus, lung, etc., or in various species. Southern analysis of cDNA libraries may also provide valuable distribution information. Standard tissue blots or species blots are commercially available. Similar techniques will be useful for evaluating diagnostic or medical conditions which may correlate with expression in various cell types.

PCR analysis using appropriate primers may also be used. Antibody analysis, including immunohistochemistry or FACS, may be used to determine cellular or tissue distribution.

Southern blot analysis of primate cDNA libraries is performed on, e.g.,: U937 premonocytic line, resting (M100); elutriated monocytes, activated with LPS, IFNγ, anti-IL-10 for 4, 16 h pooled (M106); elutriated monocytes, activated with LPS, IFNγ, IL-10 for 4, 16 h pooled (M107); elutriated monocytes, activated LPS for 1 h

(M108); elutriated monocytes, activated LPS for 6 h (M109); dendritic cells (DC) 30% CD1a+, from CD34+ GM-CSF, TNFα 12 days, resting; DC 70% CD1a+, from CD34+ GM-CSF, TNFα 12 days, resting (D101); DC 70% CD1a+, from CD34+ GM-CSF, TNFα 12 days, activated with PMA and ionomycin for 1 hr (D102); DC 70% CD1a+, from CD34+ GM-CSF, TNFα 12 days, activated with PMA and ionomycin for 6 hr (D103); DC 95% CD1a+, from CD34+ GM-CSF, TNFα 12 days activated with PMA and ionomycin for 1 or 6 hr, pooled; DC from monocytes GM-CSF, IL-4 5 days, resting (D107); DC from monocytes GM-CSF, IL-4 5 days, resting (D108); DC from monocytes GM-CSF, IL-4 5 days, activated TNFα, monocyte supe for 4, 16 h pooled (D110); EBV transfected B cell lines, resting; spleenocytes, resting; spleenocytes, activated with PMA and ionomycin; 20 NK clones resting, pooled; 20 NK clones activated with PMA and ionomycin, pooled; NKL clone, IL-2 treated; NK cytotoxic clone, resting; adipose tissue fetal 28 wk male (O108); brain fetal 28 wk male (O104); gallbladder fetal 28 wk male (O106); heart fetal 28 wk male (O103); small intestine fetal 28 wk male (O107); kidney fetal 28 wk male (O100); liver fetal 28 wk male (O102); lung fetal 28 wk male (O101); ovary fetal 25 wk female (O109); adult placenta 28 wk (O113); spleen fetal 28 wk male (O112); testes fetal 28 wk male (O111); uterus fetal 25 wk female (O110); TH0 clone Mot 72, resting (T102); T cell, TH0 clone Mot 72, activated with anti-CD28 and anti-CD3 for 3, 6, 12 h pooled (T103); T cell, TH0 clone Mot 72, anergic treated with specific peptide for 2, 7, 12 h pooled (T104); Th0 subtraction of resting from activated; T cell, TH1 clone HY06, resting (T107); T cell, TH1 clone HY06, activated with anti-CD28 and anti-CD3 for 3, 6, 12 h pooled (T108); T cell, TH1 clone HY06, anergic treated with specific peptide for 2, 6, 12 h pooled (T109); Th1 subtraction of resting from activated; T cell, TH2 clone HY935, resting (T110); T cell, TH2 clone HY935, activated with anti-CD28 and anti-CD3 for 2, 7, 12 h pooled (T111); and Th2 subtraction of resting from activated.

Samples for mouse mRNA distribution may include, e.g.,: resting mouse fibroblastic L cell line (C200); Braf:ER (Braf

fusion to estrogen receptor) transfected cells, control (C201); T cells, TH1 polarized (Mel14 bright, CD4+ cells from spleen, polarized for 7 days with IFN-γ and anti IL-4; T200); T cells, TH2 polarized (Mel14 bright, CD4+ cells from spleen, polarized for 7 days with IL-4 and anti-IFN-γ; T201); T cells, highly TH1 polarized (see Openshaw, et al. (1995) J. Exp. Med. 182:1357-1367; activated with anti-CD3 for 2, 6, 16 h pooled; T202); T cells, highly TH2 polarized (see Openshaw, et al. (1995) J. Exp. Med. 182:1357-1367; activated with anti-CD3 for 2, 6, 16 h pooled; T203); CD44- CD25+ pre T cells, sorted from thymus (T204); TH1 T cell clone D1.1, resting for 3 weeks after last stimulation with antigen (T205); TH1 T cell clone D1.1, 10 µg/ml ConA stimulated 15 h (T206); TH2 T cell clone CDC35, resting for 3 weeks after last stimulation with antigen (T207); TH2 T cell clone CDC35, 10 µg/ml ConA stimulated 15 h (T208); Mel 14+ naive T cells from spleen, resting (T209); Mel14+ T cells, polarized to Th1 with IFN-γ/IL-12/anti-IL-4 for 6, 12, 24 h pooled (T210); Mel 14+ T cells, polarized to Th2 with IL-4/anti-IFN-γ for 6, 13, 24 h pooled (T211); unstimulated mature B cell leukemia cell line A20 (B200); unstimulated B cell line CH12 (B201); unstimulated large B cells from spleen (B202); B cells from total spleen, LPS activated (B203); metrizamide enriched dendritic cells from spleen, resting (D200); dendritic cells from bone marrow, resting (D201); monocyte cell line RAW 264.7 activated with LPS 4 h (M200); bone-marrow macrophages derived with GM and M-CSF (M201); macrophage cell line J774, resting (M202); macrophage cell line J774 + LPS + anti-IL-10 at 0.5, 1, 3, 6, 12 h pooled (M203); macrophage cell line J774 + LPS + IL-10 at 0.5, 1, 3, 5, 12 h pooled (M204); aerosol challenged mouse lung tissue, Th2 primers, aerosol OVA challenge 7, 14, 23 h pooled (see Garlisi, et al. (1995) Clinical Immunology and Immunopathology 75:75-83; X206); Nippostrongulus-infected lung tissue (see Coffman, et al. (1989) Science 245:308-310; X200); total adult lung, normal (O200); total lung, rag-1 (see Schwarz, et al. (1993) Immunodeficiency 4:249-252; O205); IL-10 K.O. spleen (see Kuhn, et

al. (1991) Cell 75:263-274; X201); total adult spleen, normal (O201); total spleen, rag-1 (O207); IL-10 K.O. Peyer's patches (O202); total Peyer's patches, normal (O210); IL-10 K.O. mesenteric lymph nodes (X203); total mesenteric lymph nodes, normal (O211); IL-10 K.O. colon (X203); total colon, normal (O212); NOD mouse pancreas (see Makino, et al. (1980) Jikken Dobutsu 29:1-13; X205); total thymus, rag-1 (O208); total kidney, rag-1 (O209); total heart, rag-1 (O202); total brain, rag-1 (O203); total testes, rag-1 (O204); total liver, rag-1 (O206); rat normal joint tissue (O300); and rat arthritic joint tissue (X300).

A. Direct protein detection by antibodies

Various cells, tissues, and developmental stages are stained with labeled antibodies. The detection may be immuno-histochemical for solid tissue, by FACS in disperse cells, and by other appropriate methods for other sample types. Antibodies specific for the various forms may be used to distinguish between membrane associated and soluble fragments. Various amplification means may be coupled to increase sensitivity.

B. Functional detection

Specific neutralizing antibodies should provide means to specifically block the biological activity of the prostaglandin transporter. Activities related to prostaglandin binding, or to prostaglandin transport may be measured by sensitive means based upon knowledge of the normal biological function of the various forms.

Further testing of populations of cells, e.g., hematopoietic progenitors, or of other cell or tissue types will be useful to further determine distribution and likely function. Other tissue types, at defined developmental stages, and pathology samples may be screened to determine whether pathological states or stages may be advantageously correlated with the biological activity of the transporter.

VII. Protein Expression

PCR is used to make a construct comprising the open reading frame, preferably in operable association with proper promoter, selection, and regulatory sequences. The resulting expression

plasmid is transformed into an appropriate cell type, e.g., the Topp5, E. coli strain (Stratagene, La Jolla, CA). Ampicillin resistant (50 μg/ml) transformants are grown in Luria Broth (Gibco) at 37° C until the optical density at 550 nm is 0.7. Recombinant protein is induced with 0.4 mM isopropyl-βD-thiogalacto-pyranoside (Sigma, St. Louis, MO) and incubation of the cells continued at 20° C for a further 18 hours. Cells from a 1 liter culture are harvested by centrifugation and resuspended, e.g., in 200 ml of ice cold 30% sucrose, 50 mM Tris HCl pH 8.0, 1 mM ethylenediaminetetraacetic acid. After 10 min on ice, ice cold water is added to a total volume of 2 liters. After 20 min on ice, cells are removed by centrifugation and the supernatant is clarified by filtration via a 5 μM Millipak 60 (Millipore Corp., Bedford, MA).

The recombinant protein is purified via standard purification methods, e.g., various ion exchange chromatography methods. Immunoaffinity methods using antibodies described below can also be used. Affinity methods may be used where an epitope tag is engineered into an expression construct.

Similar methods are used to prepare expression constructs and cells in eukaryotic cells. Eukaryotic promoters and expression vectors may be produced, as described above.

Further study of the expression and control of prostaglandin transporter will be pursued. The controlling elements associated with the antigens may exhibit differential developmental, tissue specific, or other expression patterns. Upstream or downstream genetic regions, e.g., control elements, are of interest.

Multiple transfected cell lines are screened for one which expresses the antigen, membrane bound, or soluble forms, at a high level compared with other cells. Various cell lines are screened and selected for their favorable properties in handling. Natural protein can be isolated from natural sources, or by expression from a transformed cell using an appropriate expression vector. Purification of the expressed protein is achieved by standard procedures, or may be combined with engineered means for effective purification at high efficiency from cell lysates or supernatants. FLAG or His_6 segments can be used for such purification features.

VIII. Protein Purification

The prostaglandin transporter is isolated by a combination of affinity chromatography using the prostaglandin transporter specific binding compositions, e.g., antibody, as a specific binding reagent in combination with protein purification techniques allowing separation from other proteins and contaminants. Various detergent combinations may be tested to determine what combinations will retain biological activity while solubilizing contaminants. The purification may follow biological activity, e.g., prostaglandin binding or transport into membranes, or by ELISA or other structural binding reagents.

Similar methods are applied for purification of other polypeptides.

IX. Isolation of Homologous Genes

The described genes, e.g., cDNA, can be used as a hybridization probe to screen a library from a desired source, e.g., a primate cell cDNA library. Many different species can be screened both for stringency necessary for easy hybridization, and for presence using a probe. Appropriate hybridization conditions will be used to select for clones exhibiting specificity of cross hybridization.

cDNA libraries from the desired species are collected, from appropriate cell types. Screening by hybridization or PCR using degenerate probes based upon the peptide sequences will also allow isolation of appropriate clones. Alternatively, use of appropriate primers for PCR screening will yield enrichment of appropriate nucleic acid clones.

Similar methods are applicable to isolate either species, polymorphic, or allelic variants. Species variants are isolated using cross-species hybridization techniques based upon isolation of a full length isolate or fragment from one species as a probe.

Alternatively, antibodies raised against proteins will be used to screen for cells which express cross-reactive proteins from an appropriate, e.g., cDNA library. The purified protein or defined peptides are useful for generating antibodies by standard

methods, as described above. Synthetic peptides or purified protein are presented to an immune system to generate monoclonal or polyclonal antibodies. See, e.g., Coligan (1991) Current Protocols in Immunology Wiley/Greene; and Harlow and Lane (1989) Antibodies: A Laboratory Manual Cold Spring Harbor Press. The resulting antibodies are used, e.g., for screening, panning, or sorting.

X. Antibody Preparation

Synthetic peptides or purified protein, natural or recombinant, are presented to an immune system to generate monoclonal or polyclonal antibodies. See, e.g., Coligan (1991) Current Protocols in Immunology Wiley/Greene; and Harlow and Lane (1989) Antibodies: A Laboratory Manual Cold Spring Harbor Press. Polyclonal serum, or hybridomas may be prepared. In appropriate situations, the binding reagent is either labeled as described above, e.g., fluorescence or otherwise, or immobilized to a substrate for panning methods.

XI. Chromosome Mapping

DNA isolation, restriction enzyme digestion, agarose gel electrophoresis, Southern blot transfer and hybridization are performed according to standard techniques. See Jenkins, et al. (1982) J. Virol. 43:26-36. Blots may be prepared with Hybond-N nylon membrane (Amersham). The probe is labeled with ^{32}P-dCTP; washing is done to a final stringency, e.g., of 0.1X SSC, 0.1% SDS, 65° C.

Alternatively, a BIOS Laboratories (New Haven, CT) mouse somatic cell hybrid panel may be combined with PCR methods. See Fan, et al. (1996) Immunogenetics 44:97-103.

Chromosome spreads are prepared. In situ hybridization is performed on chromosome preparations obtained from phytohemagglutinin-stimulated human lymphocytes cultured for 72 h. 5-bromodeoxyuridine is added for the final seven hours of culture (60 µg/ml of medium), to ensure a posthybridization chromosomal banding of good quality.

A PCR fragment, amplified with the help of primers, is cloned into an appropriate vector. The vector is labeled by nick-translation with ^3H. The radiolabeled probe is hybridized to metaphase spreads at final concentration of 200 ng/ml of hybridization solution as described in Mattei, et al. (1985) Hum. Genet. 69:327-331.

After coating with nuclear track emulsion (KODAK NTB_2), slides are exposed. To avoid any slipping of silver grains during the banding procedure, chromosome spreads are first stained with buffered Giemsa solution and metaphase photographed. R-banding is then performed by the fluorochrome-photolysis-Giemsa (FPG) method and metaphases rephotographed before analysis.

Using these techniques, the DC-PGT gene was mapped to marker SHGC-3911 on chromosome 11q13 with a resulting lod score of 1000.0. Other markers in the SHGC-3911 region at chromosome 11q13 include the FcεRI receptor which is alleged to be associated with allergic conditions. In comparison to the location of DC-PGT, the ubiquitously expressed human PGT homologue of Lu et al., (described above) is localized to chromosome 7.

XII. Biochemical Characterization

Constructs for the expression of, e.g., DC-PGT are made with a tag (FLAG) sequence (Hopp, et al. (1988) Biotechnology (NY) 6:1205-1210) introduced in the protein. The open reading frame of the DC-PGT cDNA of SEQ ID NO: 1 is amplified by appropriate PCR primers using standard methods to introduce the FLAG peptide sequence (IBI, New Haven, CT) at the C-terminus of the protein. For example, a PFU enzyme (Stratagene) with 12 cycles PCR: 94° C 30 sec; 55° C 1 min; 72° C 4 min. PCR constructs are cloned into a PME18X vector (DNAX) using XhoI and XbaI sites incorporated into the 5' and 3' primers, respectively.

COS-7 cells are maintained in DMEM, 10% FCS, 4 mM L-glutamine (JRH Biosciences, Lenexa, KS), 100 U/ml penicillin, and 100 µg/ml streptomycin. Plasmid DNA is transfected by electroporation (BIORAD, Hercules, CA) (20 µg / 1 x 10^7 cells) and plated into tissue culture dishes. The medium is replaced after 24 hours and

cell lysates and media are collected three days after transfection. Lysis buffer (25 mM Hepes pH 7.5, 2 mM EDTA, 1.0% NP-40, 150 mM NaCl, 0.01% Aprotinin (Sigma, St. Louis, MO), 0.01% Leupeptin (Sigma)) is added to the plates. Plates are kept on ice for 45 minutes. Lysates are centrifuged for 15 minutes to eliminate cell debris. Supernatants of centrifuged cell lysates and sterile-filtered media from cultured cells are incubated with anti-FLAG M2 Affinity Gel (IBI) at 4° C overnight and washed four times with PBS. Immunoprecipitates are eluted in a Econocolumn (BIORAD) with 2.5 M Glycine, pH 2.5. Eluates are neutralized with Hepes, pH 7.4 (JRH Biosciences) and concentrated by precipitation with 24% TCA and 2% deoxycholic sodium salt (Sigma). Pellets are eluted in 2 x Sample Buffer (NOVEX, San Diego, CA), electrophoresed on 4-20% tris-glycine gels (Novex) and transferred to PVDF membranes (Immobilon-P, Millipore Corporation, Bedford, MA). Membranes are exposed to 3% non-fat milk for 1 h at 37° C. Anti-FLAG M2 antibody is used as recommended (IBI). Anti-mouse Ig horseradish peroxidase conjugate (Amersham) is used at 1:2,000 dilution and the peroxidase detection is performed with ECL detection reagents (Amersham).

Other fusion proteins can be produced, e.g., a recombinant prostaglandin transporter construct is prepared, e.g., as a fusion product with a useful affinity reagent, e.g., FLAG peptide. This peptide segment may be useful for purifying the expression product of the construct. See, e.g., Crowe, et al. (1992) OIAexpress: The High Level Expression & Protein Purification System QUIAGEN, Inc. Chatsworth, CA; and Hopp, et al. (1988) Bio/Technology 6:1204-1210. Membranes comprising the transporter are assayed to determine the natural prostaglandin substrate. Most likely the prostaglandin will be a uracil related prostaglandin, but may also include, at various levels of efficiency of binding or transport, pyrimidine or purine analogs. See, e.g., Goodman and Gilman (Current ed.), The Pharmacological Basis of Therapeutics; Lukovics and Zablocka Nucleoside Synthesis: Organosilicon Methods Ellis Horwood, N.Y.; Townsend, Chemistry of Nucleosides and Nucleotides, vols. 1-3, Plenum Press, N.Y.; Munch-Pertson (1983) Metabolism of Nucleotides, Nucleosides, and Prostaglandins in Microorganisms

Academic Press, NY; Gehrke (1990) Chromatography & Modification of Nucleosides vols. A, B, and C, Elsevier; Bloch (1975) Chemistry, Biology, & Clinical Uses of Nucleoside Analogs Annals NY Acad. Sci.; and Ulbricht (1964) Purines, Pyrimidines, & Nucleotides Franklin Co.

XIII. Expression Cloning; Partner Screening

A. Antibodies and flow-cytometric sorting

Expression cloning of cells transformed with an appropriate cDNA library may be sorted by FACS using antibody reagents described above. The sorted cells are isolated and expanded, and subjected to multiple selection cycles, leading to a high proportion of cells expressing the desired DNA.

B. Antibodies and staining

The antibodies to, e.g., DC-PGT, are used for screening of a library made from a cell line which expresses the polypeptide. Standard staining techniques are used to detect or sort intracellular or surface expressed ligand, or surface expressing transformed cells are screened by panning. Screening of intracellular expression is performed by various staining or immunofluorescence procedures. See also McMahan, et al. (1991) EMBO J. 10:2821-2832.

For example, on day 0, precoat 2-chamber permanox slides with 1 ml per chamber of fibronectin, 10 ng/ml in PBS, for 30 min at room temperature. Rinse once with PBS. Then plate COS cells at 2-3 x 10^5 cells per chamber in 1.5 ml of growth media. Incubate overnight at 37° C.

On day 1 for each sample, prepare 0.5 ml of a solution of 66 µg/ml DEAE-dextran, 66 µM chloroquine, and 4 µg DNA in serum free DME. For each set, a positive control is prepared, e.g., of huIL-10-FLAG cDNA at 1 and 1/200 dilution, and a negative mock. Rinse cells with serum free DME. Add the DNA solution and incubate 5 hr at 37° C. Remove the medium and add 0.5 ml 10% DMSO in DME for 2.5 min. Remove and wash once with DME. Add 1.5 ml growth medium and incubate overnight.

On day 2, change the medium. On days 3 or 4, the cells are fixed and stained. Rinse the cells twice with Hank's Buffered Saline Solution (HBSS) and fix in 4% paraformaldehyde (PFA)/glucose for 5 min. Wash 3X with HBSS. The slides may be stored at -80° C after all liquid is removed. For each chamber, 0.5 ml incubations are performed as follows. Add HBSS/saponin (0.1%) with 32 µl/ml of 1M NaN_3 for 20 min. Cells are then washed with HBSS/saponin 1X. Soluble antibody is added to cells and incubate for 30 min. Wash cells twice with HBSS/saponin. Add second antibody, e.g., Vector anti-mouse antibody, at 1/200 dilution, and incubate for 30 min. Prepare ELISA solution, e.g., Vector Elite ABC horseradish peroxidase solution, and preincubate for 30 min. Use, e.g., 1 drop of solution A (avidin) and 1 drop solution B (biotin) per 2.5 ml HBSS/saponin. Wash cells twice with HBSS/saponin. Add ABC HRP solution and incubate for 30 min. Wash cells twice with HBSS, second wash for 2 min, which closes cells. Then add Vector diaminobenzoic acid (DAB) for 5 to 10 min. Use 2 drops of buffer plus 4 drops DAB plus 2 drops of H_2O_2 per 5 ml of glass distilled water. Carefully remove chamber and rinse slide in water. Air dry for a few minutes, then add 1 drop of Crystal Mount and a cover slip. Bake for 5 min at 85-90° C.

Alternatively, the antibodies to a selected protein are used to affinity purify or sort out cells expressing the antigen. See, e.g., Sambrook et al. or Ausubel et al, which are incorporated herein by reference. The antigen is typically expressed on the cell surface.

Hybridization approaches may also be utilized to find closely related variants of the antigen based upon nucleic acid hybridization.

XIV. Screening for DC-PGT Substrate Specificity

The types of organic anions transported by DC-PGT of the present invention can be directly tested using standard methods. For example, DC-PGT cDNAs can be expressed in HeLa cell monolayers or in Xenopus oocytes to determine the ability of DC-PGT to uptake various tracer labeled substrates e.g., prostaglandins such as PGE1, PGE2, PGE2a, PGD2, thrombaxanes such as TxB2 or non-

prostaglandin anionic substrates such as glutathione, p-amino hippurate, taurochoalate, urate, unconjugated and conjugated bilirubin, and estradiol glucouronide. For example, for oocyte expression, water or complementary RNA (cRNA) that has been transcribed in vitro from DC-PGT cDNA and capped is injected into Xenopus oocytes at approximately 50 ng of cRNA per oocyte. Uptake studies are performed 2 to 3 days after injection by washing of oocytes three times in Waymouth's solution, incubating for various periods at 27°C with radioactive substrates (approx. 0.25 µCi/ml; total concentration, approx. 1 nM), washing three times with ice-cold Waymouth's solution, and lysing in 0.5 ml of 10% SDS. Oocyte-associated radioactivity is determined by liquid scintillation spectroscopy. For HeLa cell expression, cells are grown to approx. 80% confluence on 35 mm dishes then infected with recombinant vaccinia virus vTF7-3 of 10 plaque forming units per cell according to a method of Fuesst, et al.(1986) Proc. Nat'l Acad. Sci. USA 83:8122-8126. Thirty minutes after infection cells are transfected with DC-PGT cDNA (10 µg/ml) plus lipofectin (20 µg/ml) according to a method of Blakely, et al. (1991) Anal. Biochem. 194:302-310. After 3 hours of incubation, vaccinia virus an the DNA-lipofectin complex are removed, and the cells are maintained overnight in Dulbecco's modified Eagle's medium supplemented with 5% fetal bovine serum. Uptake studies are performed 19 hours after transfection. Monolayers are washed three times with culture medium without serum and incubated for various times at 27° C with radioactive substrate (0.5 µCi/ml per dish; total concentration, approx. 0.2 nM). Uptake is stopped by washing cells once with ice-cold Waymouth's solution containing 5% bovine serum albumin and then four times with Waymouth's solution alone. Cells are scrapped and the associated radioactivity is measured by liquid scintillation spectroscopy.

XV. Measuring DC-PGT Substrate Uptake Kinetics

Competitive tracer uptake kinetics using DC-PGT comparing various prostaglandins or thromboxanes (e.g., PGE1, PGE2, PGE2a, PGD2 or TxB2) are determined using standard competitive transport

assays. For example for determining time dependent uptake of tracer labeled prostaglandin uptakes into HeLa cells expressing DC-PGT clones the following ^{3}[H]-PGs final concentrations are used (New England Nuclear, Boston, MA): PGE_2: 0.7 nM (176 cpm/fmol); PGE_1: 0.6 nM (62 cpm/fmol); PGD_2: 0.9 nM (126 cpm/fmol); $PGF_{2\alpha}$: 0.6 nM (185 cpm/fmol); TXB2: 1.0 nM (114 cpm/fmol); PGI_2 analog ^{3}[H]-iloprost (Amersham Corp., Arlington Heights, IL) at 7.9 nM (14 cpm/fmol).

XVI. Determining DC-PGT uptake inhibition

Compositions inhibiting DC-PGT uptake can also be measured. For example to measure the inhibition of tracer PGE_2, uptakes at 10 min intervals (0.2 nM ^{3}[H]-PGE_2) with or without various concentrations of unlabeled prostanoids PGE_2, PGE_1, PGD_2, $PGF_{2\alpha}$, TXB2, PGI_2, (100-500 nM; Cayman Chemical, Ann Arbor MI) or inhibitors such as furosemide, probenecid, and indomethacin (10-100 µM, Sigma Chemical Co., St. Louis, MO) are determined in duplicate on a given transfection for one or two separate transfections. Since the substrate concentrations are at least 500 times less than the concentration of unlabeled prostanoids an apparent affinity constant, $K_{1/2}$ is determined from the equation: $K_{1/2} = [v_i/(v-v_i)]\ [i]$ where v = uptake without inhibitor, v_i = uptake with inhibitor, and i = inhibitor concentration as described by Neame and Richards (1972) in Elementary Kinetics of Membrane Carrier Transport, John Wiley & Sons, New York.

XVII. Screening for Agonists or Antagonists

Using a HeLa or Xenopus system, described above, or a comparable system, one of ordinary skill in the art can use the DC-PGT of the invention to screen for inhibitors or agonists of DC-PGT mediated tracer transport. The efficacy of potential antagonists can be compared with known PG transport inhibitors such as furosemide, probenecid, or indomethacin. Potential agonist or antagonist compositions are incubated, using a system as described above, for a time sufficient to allow binding of the

test composition and the DC-PGT transporter. Enhancement or decrement in measures of tracer uptake can be correlated to the specific composition being tested. Accordingly, one can identify compounds or compositions that modulate organic anion transport via the DC-PGT transporter of the invention by assessing the uptake of various anions such as prostaglandins or thrombaxanes in the presence and absence of the compound or compositions being tested. Similar methods may be used to screen for substrates for the enzymes, e.g., Dubs and cyclin E2.

XVIII. Isolation of Ligand for Receptor

A construct for expression of the product can be used as a specific binding reagent to identify its binding partner, e.g., ligand, by taking advantage of its specificity of binding, much like an antibody would be used. A receptor reagent is either labeled as described above, e.g., fluorescence or otherwise, or immobilized to a substrate for panning methods. See also Anderson, et al. (1997) Nature 390:175-179, which is incorporated herein by reference.

The binding composition is used to screen an expression library made from a cell line which expresses a binding partner, e.g., TNF family ligand. Standard staining techniques are used to detect or sort intracellular or surface expressed receptor, or surface expressing transformed cells are screened by panning. Screening of intracellular expression is performed by various staining or immunofluorescence procedures. See also McMahan, et al. (1991) EMBO J. 10:2821-2832.

Alternatively, receptor reagents are used to affinity purify or sort out cells expressing a receptor. See, e.g., Sambrook, et al. or Ausubel, et al.

Another strategy is to screen for a membrane bound ligand by panning. The cDNA containing ligand cDNA is constructed as described above. The ligand can be immobilized and used to immobilize expressing cells. Immobilization may be achieved by use of appropriate antibodies which recognize, e.g., a FLAG sequence or a receptor fusion construct, or by use of antibodies raised against the first antibodies. Recursive cycles of

selection and amplification lead to enrichment of appropriate clones and eventual isolation of ligand expressing clones.

Phage expression libraries can be screened by receptor. Appropriate label techniques, e.g., anti-FLAG antibodies, will allow specific labeling of appropriate clones.

IX. Chemotaxis Assays

Chemokine proteins are produced, e.g., in COS cells transfected with a plasmid carrying the chemokine cDNA by electroporation. See, Hara, et al. (1992) EMBO J. 10:1875-1884. Physical analytical methods may be applied, e.g., CD analysis, to compare tertiary structure to other chemokines to evaluate whether the protein has likely folded into an active conformation. After transfection, a culture supernatant is collected and subjected to bioassays. A mock control, e.g., a plasmid carrying the luciferase cDNA, is used. See, de Wet, et al. (1987) Mol. Cell. Biol. 7:725-757. A positive control, e.g., recombinant murine MIP-1α from R&D Systems (Minneapolis, MN), is typically used. Likewise, antibodies may be used to block the biological activities, e.g., as a control.

Lymphocyte migration assays are performed as previously described, e.g., in Bacon, et al. (1988) Br. J. Pharmacol. 95:966-974. Other trafficking assays are also available. See, e.g., Quidling-Järbrink, et al. (1995) Eur. J. Immunol. 25:322-327; Koch, et al. (1994) J. Clinical Investigation 93:921-928; and Antony, et al. (1993) J. Immunol. 151:7216-7223. Murine Th2 T cell clones, CDC-25 (see Tony, et al. (1985) J. Exp. Med. 161:223-241) and HDK-1 (see Cherwinski, et al. (1987) J. Exp. Med. 166:1229-1244), made available from R. Coffman and A. O'Garra (DNAX, Palo Alto, CA), respectively, are used as controls.

Ca2+ flux upon chemokine stimulation is measured according to the published procedure described in Bacon, et al. (1995) J. Immunol. 154:3654-3666.

Maximal numbers of migrating cells in response to MIP-1α typically occur at a concentration of 10^{-8} M, in agreement with

original reports for CD4+ populations of human T cells. See Schall (1993) J. Exp. Med. 177:1821-1826. A dose-response curve is determined, preferably giving a characteristic bell shaped dose-response curve.

After stimulation with CC chemokines, lymphocytes generally show a measurable intracellular Ca2+ flux. MIP-1α is capable of inducing immediate transients of calcium mobilization. Typically, the levels of chemokine used in these assays will be comparable to those used for the chemotaxis assays (1/1000 dilution of conditioned supernatants).

XX. Biological Activities

A robust and sensitive assay is selected as described above, e.g., on immune cells, neuronal cells, or stem cells. Chemokine is added to the assay in increasing doses to see if a dose response is detected. For example, in a proliferation assay, cells are plated out in plates. Appropriate culture medium is provided, and chemokine is added to the cells in varying amounts. Growth is monitored over a period of time which will detect either a direct effect on the cells, or an indirect effect of the chemokine.

Alternatively, an activation assay or attraction assay is used. An appropriate cell type is selected, e.g., hematopoietic cells, myeloid (macrophages, neutrophils, polymorphonuclear cells, etc.) or lymphoid (T cell, B cell, or NK cells), neural cells (neurons, neuroglia, oligodendrocytes, astrocytes, etc.), or stem cells, e.g., progenitor cells which differentiate to other cell types, e.g., gut crypt cells and undifferentiated cell types.

Retroviral infection assays have also been described using, e.g., the CCR1, CCR3, and CCR5 receptors. These receptors, which bind the RANTES and MIP-1 related chemokines, are likely also to be receptors for the HCC5 . Recent description of these chemokine receptors in retroviral infection processes, and the effects by the related RANTES and MIP-1 chemokines, suggest similar effects may exist with the HCC5 . See, e.g., Balter (1996) Science 272:1740 (describing evidence for chemokine receptors as coreceptors for HIV); and Deng, et al. (1996) Nature 381:661-666.

Chemokines may also be assayed for activity in hemopoietic assays as described, e.g., by H. Broxmeyer. See Bellido, et al. (1995) J. Clinical Investigation 95:2886-2895; and Jilka, et al. (1995) Expt'l Hematology 23:500-506. They may be assayed for angiogenic activities as described, e.g., by Streiter, et al. (1992) Am. J. Pathol. 141:1279-1284. Or for a role in inflammation. See, e.g., Wakefield, et al. (1996) J. Surgical Res. 64:26-31.

Other assays will include those which have been demonstrated with other chemokines. See, e.g., Schall and Bacon (1994) Current Opinion in Immunology 6:865-873; and Bacon and Schall (1996) Int. Arch. Allergy & Immunol. 109:97-109.

The DUB genes will be screened for the deubiquitinating activities, as described. See, e.g., Hochstrasser (1995) Curr. Opin. Cell Biol. 7:215-223; Wilkinson, et al. (1995) Biochemistry 34:14535-14546; Baker, et al. (1992) J. Biol. Chem. 267:23364-23375; Baek et al. (1998) J. Biol. Chem. 272:25560-25565; and Papa and Hochstrasser (1993) Nature 366:313-319. For example, for an in vitro assay for UBP Activity, ^{125}I-labeled Ub-PESTc is used as a substrate according to the method of Woo, et al.(1995) J. Biol. Chem. 270:18766-18773. Reaction mixtures (0.1 ml) contain the proper amount of the enzyme preparations and 10-30 µg of ^{125}I-labeled Ub-PESTc in 100 mM Tris-HCl (pH 7.8), 1 mM dithiothreitol, 1 mM EDTA, and 5% glycerol. After incubating the mixtures for appropriate periods, the reaction is terminated by adding 50 µl of 40% (w/v) trichloroacetic acid and 50 µl of 1.2% (w/v) bovine serum albumin. The samples are centrifuged, and the resulting supernatants are counted for their radioactivities using a counter. The enzyme activity is expressed as a percentage of ^{125}I-labeled Ub-PESTc hydrolyzed to acid-soluble products. When assaying the hydrolysis of Ub-NH-carboxyl extension proteins and His-di-Ub, incubations are performed as above but in the presence of 5 µg of the substrate. After incubation for appropriate periods, the samples are subjected to discontinuous gel electrophoresis as described by Baek, et al. (1998) J. Biol. Chem.

272:25560-25565. Proteins in the gels were then visualized by staining with Coomassie Blue R-250 or by exposing to x-ray films (Fuji) at 70° C.. To prepare ^{125}I-labeled poly-Ub-NH-lysozyme conjugates, 2 µg of the ^{125}I-labeled lysozyme (5 x 10^5 cpm) are incubated with 10 µg of Ub, 120 µg of fraction II, and an ATP-regenerating system consisting of 10 mM Tris-HCl (pH 7.8), 15 units/ml creatine phosphokinase, 6.5 mM phosphocreatine, 1.5 mM ATP, 1 mM dithiothreitol, 0.5 mM $MgCl_2$, and 1 mM KCl in a final volume of 0.05 ml. Incubations are performed for 2 h at 37° C in the presence of 1 mM hemin to prevent proteolysis of the ubiquitinated protein conjugates by the 26 S proteosome. After incubation, the samples are heated for 10 min at 55° C for inactivation of endogenous UBPs. Alternatively, Dub11 or Dub12 can be expressed as a GST fusion protein according to the method of Zhu, et al. (1997) J. Biol. Chem. 272:51-57 by cloning into an appropriate expression vector and subsequently co-transformed with a plasmid encoding Ub-Met-β-gal, in which ubiquitin is fused to the NH_2 terminus of β-galactosidase and testing for cleavage.

However, the deubiquitinating enzymes have also been reported to have additional functions besides deubiquitination. See, e.g., Hochstrasser (1996) Cell 84:813-815; Hicke and Riezman (1996) Cell 84:277-287; and Chen, et al. (1996) Cell 84:853-862.

The MD gene products will be screened for cell signaling activities. See, e.g., Miyake, et al. (1998) J. Immunol. 161:1348-1353; Kobe and Deisenhofer (1994) Trends Biochem. Sci. 19:412.

XXI. Antagonizing cyclin E2 proteins

The inhibition of cell cycle progression is especially important for the control of abnormally proliferative diseases, e.g., cancer. Several methods are available to accomplish this control. The ability of cyclin binding is inhibited by the use, e.g., of antibodies raised against the cyclin binding proteins. Other elements include, e.g., peptidomimetics which are peptides designed to mimic the binding site of cyclin associated proteins and disrupt the interaction of these proteins with cyclin. The

most effective method to block cell cycle progression is the use of small molecules, e.g., to block the interaction of the associated proteins with cyclin, or to block downstream activity of the associated proteins, as described, e.g., in Hung, et al. (1996) Chemistry and Biology 3:623-639. Exposure of a cell to these permeable small molecules should cause a conditional loss of function of the target protein.

Also included in this category is the use of gene therapy to block the expression of the cyclin associated protein or gene transcription factors. Methods of using gene therapy are described, e.g., in Goodnow (1992) "Transgenic Animals" in Roitt (ed.) Encyclopedia of Immunology, Academic Press, San Diego, pp. 1502-1504; Travis (1992) Science 256:1392-1394; Kuhn, et al. (1991) Science 254:707-710; Capecchi (1989) Science 244:1288; Robertson (1987) (ed.) Teratocarcinomas and Embryonic Stem Cells: A Practical Approach, IRL Press, Oxford; and Rosenberg (1992) J. Clinical Oncology 10:180-199. Also included is the use of antisense RNA in gene therapy to block expression of the target gene, or proper splicing of gene transcripts.

All citations herein are incorporated herein by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

Many modifications and variations of this invention can be made without departing from its spirit and scope, as will be apparent to those skilled in the art. The specific embodiments described herein are offered by way of example only, and the invention is to be limited by the terms of the appended claims, along with the full scope of equivalents to which such claims are entitled.

WHAT IS CLAIMED IS:

1. An isolated or recombinant antigenic polypeptide comprising:

a) a plurality of distinct segments, wherein each said segment has identity to at least 12 contiguous amino acids from the mature SEQ ID NO: 2; or

b) at least 17 contiguous amino acids from the mature SEQ ID NO: 2.

2. The polypeptide of Claim 1, wherein said plurality of segments includes

a) one of at least 19 contiguous amino acids; or

b) two of at least 15 contiguous amino acids.

3. The polypeptide of Claim 1, wherein said polypeptide:

a) comprises the mature SEQ ID NO: 2;

b) binds with specificity to a polyclonal antibody which specifically binds to SEQ ID NO: 2; or

c) said polypeptide:

i) is a natural allelic variant of SEQ ID NO: 2;

ii) is at least 30 amino acids in length;

iii) exhibits at least two non-overlapping epitopes specific for SEQ ID NO: 2;

iv) is a synthetic polypeptide;

v) is attached to a solid substrate; or

vi) is a 5-fold or less conservative substitution from SEQ ID NO: 2.

4. A fusion protein comprising first and second portions, said first portion comprising a polypeptide of Claim 1 and said second portion comprising a detectable marker.

5. A pharmaceutical composition comprising a sterile polypeptide of Claim 1 in a pharmaceutically acceptable carrier.

6. An isolated or recombinant polynucleotide encoding a polypeptide of Claim 1.

7. The polynucleotide of Claim 6, which:

a) comprises the mature polypeptide coding portion of SEQ ID NO: 1; or

b) encodes the mature SEQ ID NO: 2.

8. The polynucleotide of Claim 6, wherein said polynucleotide is:

a) a PCR product;

b) a hybridization probe;

c) a mutagenesis primer; or

d) made by chemical synthesis.

9. The polynucleotide of Claim 6, which is:

a) detectably labeled;

b) a deoxyribonucleic acid; or

c) double stranded.

10. An expression vector comprising a polynucleotide of Claim 6.

11. The vector of Claim 10, wherein said polypeptide specifically binds polyclonal antibodies generated against an immunogen of mature SEQ ID NO: 2.

12. The vector of Claim 10, which

a) selectively hybridizes under stringent hybridization conditions to a target polynucleotide sequence having at least 60 contiguous nucleotides from SEQ ID NO: 1;

b) encodes a polypeptide having at least 50 contiguous amino acid residues from mature SEQ ID NO: 2; or

c) is suitable for transfection into a prokaryote or eukaryote host cell.

13. The vector of Claim 12, wherein said host cell is:

a) a mammalian cell;

b) a bacterial cell;

c) an insect cell;
d) a prokaryote;
e) a eukaryote; or
f) a COS cell.

14. A method of making a polypeptide comprising expressing said vector of Claim 13 in said host cell.

15. An isolated or recombinant polynucleotide which hybridizes to the coding portion of SEQ ID NO: 1 under stringent hybridization and wash conditions of at least 50° C, a salt concentration of less than 400 mM, and 50% formamide.

16. An expression vector comprising the polynucleotide of Claim 15.

17. The vector of Claim 16 which hybridizes to the coding portion of SEQ ID NO: 1 under stringent hybridization and wash conditions of at least 60° C, a salt concentration of less than 200 mM, and 50% formamide.

18. The vector of Claim 25, which encodes a polypeptide which specifically binds an antibody generated against a mature SEQ ID NO: 2.

19. The polynucleotide of Claim 15 which hybridizes to SEQ ID NO: 1, wherein said polynucleotide is:
a) a PCR product;
b) a hybridization probe;
c) a mutagenesis primer; or
d) made by chemical synthesis.

20. A method of modulating the physiology or development of a cell, comprising contacting said cell with an agonist or antagonist of a polypeptide of Claim 1.

21. A method of detecting the presence of a complementary polynucleotide in a sample, comprising contacting a polynucleotide of Claim 6 that selectively hybridizes with said complementary polynucleotide in said sample to form a detectable duplex; thereby indicating the presence of said polynucleotide in said sample.

22. A method for identifying a compound that binds to a polypeptide of Claim 1, comprising:

a) incubating components comprising said compound and said polypeptide under conditions sufficient to allow the components to interact; and

b) measuring the binding of the compound to said polypeptide.

23. An isolated or recombinant polynucleotide encoding an antigenic polypeptide comprising:

a) at least 17 contiguous amino acids from the mature polypeptide from SEQ ID NO: 6;

b) at least 17 contiguous amino acids from the mature polypeptide from SEQ ID NO: 8;

c) at least 17 contiguous amino acids from the mature polypeptide from SEQ ID NO: 10;

d) at least 17 contiguous amino acids from the mature polypeptide from SEQ ID NO: 12;

e) at least 17 contiguous amino acids from the mature polypeptide from SEQ ID NO: 17;

f) at least 17 contiguous amino acids from the mature polypeptide from SEQ ID NO: 19;

g) at least 17 contiguous amino acids from the mature polypeptide from SEQ ID NO: 21; or

h) at least 17 contiguous amino acids from the mature polypeptide from SEQ ID NO: 23.

24. The polynucleotide of Claim 23, encoding all of the polypeptide of:

a) signal processed SEQ ID NO: 6;

b) signal processed SEQ ID NO: 8;

c) signal processed SEQ ID NO: 10;

d) signal processed SEQ ID NO: 12;
e) signal processed SEQ ID NO: 17;
f) SEQ ID NO: 19;
g) SEQ ID NO: 21; or
h) SEQ ID NO: 23.

25. The polynucleotide of Claim 23, which hybridizes at 55° C, less than 500 mM salt, and 50% formamide to the:
a) mature protein coding portion of SEQ ID NO: 5;
b) signal processed coding portion of SEQ ID NO: 7;
c) signal processed coding portion of SEQ ID NO: 9;
d) signal processed coding portion of SEQ ID NO: 11;
e) mature protein coding portion of SEQ ID NO: 16;
f) polypeptide coding portion of SEQ ID NO: 18;
g) polypeptide coding portion of SEQ ID NO: 20; or
h) polypeptide coding portion of SEQ ID NO: 22.

26. The polynucleotide of Claim 25, comprising at least 35 contiguous nucleotides of:
a) mature protein coding portion of SEQ ID NO: 5;
b) signal processed coding portion of SEQ ID NO: 7;
c) signal processed coding portion of SEQ ID NO: 9;
d) signal processed coding portion of SEQ ID NO: 11;
e) mature protein coding portion of SEQ ID NO: 16;
f) polypeptide coding portion of SEQ ID NO: 18;
g) polypeptide coding portion of SEQ ID NO: 20; or
h) polypeptide coding portion of SEQ ID NO: 22.

27. An expression vector comprising the polynucleotide of Claim 23.

28. A host cell containing the expression vector of Claim 27, including a eukaryotic cell.

29. A method of making an antigenic polypeptide comprising expressing a recombinant polynucleotide of Claim 23.

30. A method for detecting a polynucleotide of Claim 23, comprising contacting said polynucleotide with a probe that hybridizes, under stringent conditions, to at least 25 contiguous nucleotides of the:

a) mature protein coding portion of SEQ ID NO: 5;
b) signal processed coding portion of SEQ ID NO: 7;
c) signal processed coding portion of SEQ ID NO: 9;
d) signal processed coding portion of SEQ ID NO: 11;
e) mature protein coding portion of SEQ ID NO: 16;
f) polypeptide coding portion of SEQ ID NO: 18;
g) polypeptide coding portion of SEQ ID NO: 20; or
h) polypeptide coding portion of SEQ ID NO: 22;

to form a duplex, wherein detection of said duplex indicates the presence of said polynucleotide.

31. A kit for the detection of a polynucleotide of Claim 23, comprising a compartment containing a probe that hybridizes, under stringent hybridization conditions, to at least 17 contiguous nucleotides of a polynucleotide of Claim b1 to form a duplex.

32. The kit of Claim 31, wherein said probe is detectably labeled.

33. A binding compound comprising an antibody binding site which specifically binds to a polypeptide comprising at least 17 contiguous amino acids from:

a) signal processed SEQ ID NO: 6;
b) signal processed SEQ ID NO: 8;
c) signal processed SEQ ID NO: 10;
d) signal processed SEQ ID NO: 12;
e) signal processed SEQ ID NO: 17;
f) SEQ ID NO: 19;
g) SEQ ID NO: 21; or
h) SEQ ID NO: 23.

34. The binding compound of Claim 33, wherein:

a) said antibody binding site is:

1) selectively immunoreactive with the:
   a) signal processed SEQ ID NO: 6;
   b) signal processed SEQ ID NO: 8;
   c) signal processed SEQ ID NO: 10;
   d) signal processed SEQ ID NO: 12;
   e) signal processed SEQ ID NO: 17;
   f) SEQ ID NO: 19;
   g) SEQ ID NO: 21; or
   h) SEQ ID NO: 23;
2) raised against a purified or recombinantly produced human HDTEA84 protein;
3) raised against a purified or recombinantly produced human HSLJD37R protein; or
4) in a monoclonal antibody, Fab, or F(ab)2; or

b) said binding compound is:
1) an antibody molecule;
2) a polyclonal antiserum;
3) detectably labeled;
4) sterile; or
5) in a buffered composition.

35. A method using the binding compound of Claim 33, comprising contacting said binding compound with a biological sample comprising an antigen, thereby forming a binding compound:antigen complex.

36. The method of Claim 35, wherein said biological sample is from a human, and wherein said binding compound is an antibody.

37. A detection kit comprising said binding compound of Claim 34, and:
a) instructional material for the use of said binding compound for said detection; or
b) a compartment providing segregation of said binding compound.

38. A substantially pure or isolated antigenic polypeptide, which binds to said binding composition of Claim 33, and further comprises at least 17 contiguous amino acids from:

a) signal processed SEQ ID NO: 6;
b) signal processed SEQ ID NO: 8;
c) signal processed SEQ ID NO: 10;
d) signal processed SEQ ID NO: 12;
e) signal processed SEQ ID NO: 17;
f) SEQ ID NO: 19;
g) SEQ ID NO: 21; or
h) SEQ ID NO: 23.

39. The polypeptide of Claim 38, which:

a) comprises at least a fragment of at least 25 contiguous amino acid residues from a primate HDTEA84 protein;
b) comprises at least a fragment of at least 25 contiguous amino acid residues from a primate HSLJD37R protein;
c) comprises at least a fragment of at least 25 contiguous amino acid residues from a rodent or primate RANKL protein;
d) is a soluble polypeptide;
e) is detectably labeled;
f) is in a sterile composition;
g) is in a buffered composition;
h) binds to an sialic acid residue;
i) is recombinantly produced, or
j) has a naturally occurring polypeptide sequence.

40. The polypeptide of Claim 39, which comprises at least 17 contiguous amino acids from the:

a) signal processed SEQ ID NO: 6;
b) signal processed SEQ ID NO: 8;
c) signal processed SEQ ID NO: 10;
d) signal processed SEQ ID NO: 12;
e) signal processed SEQ ID NO: 17;
f) SEQ ID NO: 19;
g) SEQ ID NO: 21; or
h) SEQ ID NO: 23.

41. A method of modulating a precursor cell physiology or function comprising a step of contacting said cell with:

a) a binding compound which binds to said polypeptide of Claim 38;

b) an HDTEA84 polypeptide;

c) an HSLJD37R polypeptide; or

d) a RANKL polypeptide.

42. The method of Claim 41, wherein said contacting is in combination with a TNF family ligand, or an antagonist of said TNF family ligand.

43. A composition of matter selected from:

a) a substantially pure or recombinant HCC5 polypeptide exhibiting identity over a length of at least 12 amino acids to SEQ ID NO: 25;

b) an isolated natural sequence HCC5 of mature SEQ ID NO: 25;

c) a fusion protein comprising HCC5 sequence;

d) a substantially pure or recombinant Dub11 polypeptide exhibiting identity over a length of at least about 12 amino acids to SEQ ID NO: 32 or 34;

e) an isolated natural sequence Dub11 of mature SEQ ID NO: 32 or 34;

f) a fusion protein comprising Dub11 sequence;

g) a substantially pure or recombinant Dub12 polypeptide exhibiting identity over a length of at least about 12 amino acids to SEQ ID NO: 36 or 38;

h) an isolated natural sequence Dub12 of mature SEQ ID NO: 36 or 38;

i) a fusion protein comprising Dub12 sequence;

j) a substantially pure or recombinant MD-1 polypeptide exhibiting identity over a length of at least about 12 amino acids to SEQ ID NO: 42;

k) an isolated natural sequence MD-1 of mature SEQ ID NO: 42;

l) a fusion protein comprising primate MD-1 sequence;
m) a substantially pure or recombinant MD-2 polypeptide exhibiting identity over a length of at least about 12 amino acids to SEQ ID NO: 44 or 46;
n) an isolated natural sequence MD-2 of mature SEQ ID NO: 44 or 46;
o) a fusion protein comprising primate MD-2 sequence;
p) a substantially pure or recombinant MD-2 polypeptide exhibiting identity over a length of at least about 12 amino acids to SEQ ID NO: 48 or 49;
q) an isolated natural sequence MD-2 of mature SEQ ID NO: 48; or
r) a fusion protein comprising murine MD-2 sequence.

44. The composition of Claim 43, which is a substantially pure or isolated:
a) a HCC5 polypeptide, wherein said length is at least 17 amino acids;
b) a Dub11 polypeptide, wherein said length is at least 17 amino acids;
c) a Dub12 polypeptide, wherein said length is at least 17 amino acids;
d) a primate MD-1 polypeptide, wherein said length is at least 17 amino acids;
e) a primate MD-2 polypeptide, wherein said length is at least 17 amino acids; or
f) a rodent MD-2 polypeptide, wherein said length is at least 17 amino acids.

45. The composition of Claim 44, which is a substantially pure or isolated:
a) a HCC5 polypeptide, wherein said length is at least 21 amino acids;
b) a Dub11 polypeptide, wherein said length is at least 21 amino acids;
c) a Dub12 polypeptide, wherein said length is at least 21 amino acids;

d) a primate MD-1 polypeptide, wherein said length is at least 21 amino acids;

e) a primate MD-2 polypeptide, wherein said length is at least 21 amino acids; and

f) a rodent MD-2 polypeptide, wherein said length is at least 21 amino acids.

46. The composition of matter of Claim 43, wherein said:

a) HCC5 polypeptide:

i) is from a primate, including a human;

ii) comprises at least one polypeptide segment of SEQ ID NO: 25;

iii) exhibits a plurality of portions exhibiting said identity;

iv) is a natural allelic variant of HCC5;

v) has a length at least about 30 amino acids;

vi) exhibits at least two non-overlapping epitopes which are specific for a primate HCC5;

vii) exhibits a sequence identity over a length of at least 35 amino acids to a HCC5;

viii) is glycosylated;

ix) is a synthetic polypeptide;

x) is attached to a solid substrate;

xi) is conjugated to another chemical moiety;

xii) is a 5-fold or less substitution from natural sequence; or

xiii) is a deletion or insertion variant from a natural sequence;

b) Dub11 polypeptide:

i) is from a primate, including a human;

ii) comprises at least one polypeptide segment of SEQ ID NO: 32 or 34;

iii) exhibits a plurality of portions exhibiting said identity;

iv) is a natural allelic variant of Dub11;

v) has a length at least about 30 amino acids;

vi) exhibits at least two non-overlapping epitopes which are specific for a primate Dub11;
vii) exhibits a sequence identity over a length of at least about 35 amino acids to a Dub11;
viii) is glycosylated;
ix) is a synthetic polypeptide;
x) is attached to a solid substrate;
xi) is conjugated to another chemical moiety;
xii) is a 5-fold or less substitution from natural sequence; or
xiii) is a deletion or insertion variant from a natural sequence;

c) Dub12 polypeptide:
i) is from a primate, including a human;
ii) comprises at least one polypeptide segment of SEQ ID NO: 36 or 38;
iii) exhibits a plurality of portions exhibiting said identity;
iv) is a natural allelic variant of Dub12;
v) has a length at least about 30 amino acids;
vi) exhibits at least two non-overlapping epitopes which are specific for a primate Dub12;
vii) exhibits a sequence identity over a length of at least about 35 amino acids to a Dub12;
viii) is glycosylated;
ix) is a synthetic polypeptide;
x) is attached to a solid substrate;
xi) is conjugated to another chemical moiety;
xii) is a 5-fold or less substitution from natural sequence; or
xiii) is a deletion or insertion variant from a natural sequence;

d) primate MD-1 polypeptide:
i) is from a human;
ii) comprises at least one polypeptide segment of SEQ ID NO: 42;

iii) exhibits a plurality of portions exhibiting said identity;
iv) is a natural allelic variant of primate MD-1;
v) has a length at least about 30 amino acids;
vi) exhibits at least two non-overlapping epitopes which are specific for a primate MD-1;
vii) exhibits a sequence identity over a length of at least about 35 amino acids to a primate MD-1;
viii) is glycosylated;
ix) is a synthetic polypeptide;
x) is attached to a solid substrate;
xi) is conjugated to another chemical moiety;
xii) is a 5-fold or less substitution from natural sequence; or
xiii) is a deletion or insertion variant from a natural sequence;

e) primate MD-2 polypeptide::
i) is from a human;
ii) comprises at least one polypeptide segment of SEQ ID NO: 44 or 46;
iii) exhibits a plurality of portions exhibiting said identity;
iv) is a natural allelic variant of primate MD-2;
v) has a length at least about 30 amino acids;
vi) exhibits at least two non-overlapping epitopes which are specific for a primate MD-2;
vii) exhibits a sequence identity over a length of at least about 35 amino acids to a primate MD-2;
viii) is glycosylated;
ix) is a synthetic polypeptide;
x) is attached to a solid substrate;
xi) is conjugated to another chemical moiety;
xii) is a 5-fold or less substitution from natural sequence; or
xiii) is a deletion or insertion variant from a natural sequence; or

f) rodent MD-2 polypeptide:

i) is from a mouse;
ii) comprises at least one polypeptide segment of SEQ ID NO: 48 or 49;
iii) exhibits a plurality of portions exhibiting said identity;
iv) is a natural allelic variant of rodent MD-2;
v) has a length at least about 30 amino acids;
vi) exhibits at least two non-overlapping epitopes which are specific for a rodent MD-2;
vii) exhibits a sequence identity over a length of at least about 35 amino acids to a rodent MD-2;
viii) is glycosylated;
ix) is a synthetic polypeptide;
x) is attached to a solid substrate;
xi) is conjugated to another chemical moiety;
xii) is a 5-fold or less substitution from natural sequence; or
xiii) is a deletion or insertion variant from a natural sequence.

47. A composition comprising a sterile polypeptide of Claim 43, wherein said polypeptide is:
a) HCC5 polypeptide;
b) Dub11 polypeptide;
c) Dub12 polypeptide;
d) MD-1 polypeptide; or
e) MD-2 polypeptide.

48. A composition of Claim 43 comprising:
a) said HCC5 polypeptide and:
1) a carrier, wherein said carrier is:
a) an aqueous compound, including water, saline, and/or buffer; and/or
b) formulated for oral, rectal, nasal, topical, or parenteral administration;
2) another chemokine, including one selected from the group of HCC1, HCC2, HCC3, and HCC4; or

3) an antibody antagonist for a chemokine, including one selected from the group of HCC1, HCC2, HCC3, and HCC4;

b) said Dub11 polypeptide and a carrier, wherein said carrier is

a) an aqueous compound, including water, saline, and/or buffer; and/or

b) formulated for oral, rectal, nasal, topical, or parenteral administration;

c) said Dub12 polypeptide and a carrier, wherein said carrier is:

a) an aqueous compound, including water, saline, and/or buffer; and/or

b) formulated for oral, rectal, nasal, topical, or parenteral administration;

d) said MD-1 polypeptide and a carrier, wherein said carrier is:

a) an aqueous compound, including water, saline, and/or buffer; and/or

b) formulated for oral, rectal, nasal, topical, or parenteral administration;

e) said MD-2 polypeptide and a carrier, wherein said carrier is:

a) an aqueous compound, including water, saline, and/or buffer; and/or

b) formulated for oral, rectal, nasal, topical, or parenteral administration.

49. The fusion protein of Claim 43 comprising:

a) mature protein sequence of Table 7;

b) mature protein sequence of Table 9;

b) mature protein sequence of Table 11;

c) a detection or purification tag, including a FLAG, His6, or Ig sequence; or

d) sequence of another chemokine protein with said protein in a).

50. A kit comprising a polypeptide of Claim 43, and:

a) a compartment comprising said polypeptide; and/or

b) instructions for use or disposal of reagents in said kit.

51. A binding compound comprising an antigen binding portion from an antibody, which specifically binds to a natural:

a) HCC5 polypeptide of Claim 43, wherein said antibody:

i) is raised against a peptide sequence of a mature polypeptide sequence of Table 7;

ii) is raised against a mature HCC5;

iii) is raised to a purified HCC5;

iv) is immunoselected;

v) is a polyclonal antibody;

vi) binds to a denatured HCC5; or

vii) exhibits a Kd to antigen of at least 30 μM;

b) Dub11 polypeptide of Claim 43, wherein said antibody:

i) is raised against a peptide sequence of a mature polypeptide sequence of Table 9;

ii) is raised against a mature Dub11;

iii) is raised to a purified Dub11;

iv) is immunoselected;

v) is a polyclonal antibody;

vi) binds to a denatured Dub11; or

vii) exhibits a Kd to antigen of at least 30 μM;

c) Dub12 polypeptide of Claim 43, wherein said antibody:

i) is raised against a peptide sequence of a mature polypeptide sequence of Table 9;

ii) is raised against a mature Dub12;

iii) is raised to a purified Dub12;

iv) is immunoselected;

v) is a polyclonal antibody;

vi) binds to a denatured Dub12; or

vii) exhibits a Kd to antigen of at least 30 μM;

d) a primate MD-1 polypeptide of Claim 43, wherein said antibody:

i) is raised against a peptide sequence of a mature polypeptide sequence of Table 11;
ii) is raised against a mature MD-1;
iii) is raised to a purified MD-1;
iv) is immunoselected;
v) is a polyclonal antibody;
vi) binds to a denatured MD-1; or
vii) exhibits a Kd to antigen of at least 30 μM;

e) a primate MD-2 polypeptide of Claim 43, wherein said antibody:
i) is raised against a peptide sequence of a mature polypeptide sequence of Table 11;
ii) is raised against a mature MD-2;
iii) is raised to a purified MD-2;
iv) is immunoselected;
v) is a polyclonal antibody;
vi) binds to a denatured MD-2; or
vii) exhibits a Kd to antigen of at least 30 μM; or

f) a rodent MD-2 polypeptide of Claim 43, wherein said antibody:
i) is raised against a peptide sequence of a mature polypeptide sequence of Table 11;
ii) is raised against a mature rodent MD-2;
iii) is raised to a purified rodent MD-2;
iv) is immunoselected;
v) is a polyclonal antibody;
vi) binds to a denatured rodent MD-2; or
vii) exhibits a Kd to antigen of at least 30 μM.

52. The binding composition of Claim 51, wherein:
a) said polypeptide is from a primate or rodent;
b) said binding compound is an Fv, Fab, or Fab2 fragment;
c) said binding compound is conjugated to another chemical moiety;
d) is attached to a solid substrate, including a bead or plastic membrane;

e) is in a sterile composition; or
f) is detectably labeled, including a radioactive or fluorescent label.

53. A kit comprising said binding compound of Claim 51, and:
a) a compartment comprising said binding compound;
b) a compartment comprising purified antigen; and/or
c) instructions for use or disposal of reagents in said kit.

54. A method of producing an antigen:antibody complex, comprising contacting an antibody of Claim 51 and:
a) a primate HCC5 polypeptide;
b) a primate Dub11 polypeptide;
c) a primate Dub12 polypeptide;
d) a primate MD-1 polypeptide;
e) a primate MD-2 polypeptide; or
f) a rodent MD-2 polypeptide;
thereby allowing said complex to form.

55. A composition comprising said binding compound of Claim 51 and:
1) a carrier, wherein said carrier is:
a) an aqueous compound, including water, saline, and/or buffer; and/or
b) formulated for oral, rectal, nasal, topical, or parenteral administration; or
2) an antibody antagonist for another chemokine, including one selected from the group of HCC1, HCC2, HCC3, and HCC4.

56. An isolated or recombinant nucleic acid encoding a polypeptide or fusion protein of Claim 43, wherein:
A) said HCC5 :
a) polypeptide is from a primate, including a human; or
b) nucleic acid:
i) encodes an antigenic HCC5 peptide sequence of Table 7;

ii) encodes a plurality of antigenic peptide sequences of Table 7;

iii) exhibits identity over at least 25 nucleotides to a natural cDNA encoding said HCC5 segment;

iv) is a hybridization probe for a gene encoding said HCC5 polypeptide; or

v) further encodes another chemokine, including one selected from the group of HCC1, HCC2, HCC3, and HCC4;

B) said Dub11:

a) polypeptide is from a primate, including a human; or

b) nucleic acid:

i) encodes an antigenic Dub11 peptide sequence of Table 9;

ii) encodes a plurality of antigenic peptide sequences of Table 9;

iii) exhibits identity over at least 25 nucleotides to a natural cDNA encoding said Dub11 segment; or

iv) is a hybridization probe for a gene encoding said Dub11 polypeptide;

C) said Dub12:

a) polypeptide is from a primate, including a human; or

b) nucleic acid:

i) encodes an antigenic Dub12 peptide sequence of Table 9;

ii) encodes a plurality of antigenic peptide sequences of Table 9;

iii) exhibits identity over at least 25 nucleotides to a natural cDNA encoding said Dub12 segment;

iv) is a hybridization probe for a gene encoding said Dub12 polypeptide;

D) said primate MD-1:

a) polypeptide is from a primate, including a human; or

b) nucleic acid:

i) encodes an antigenic MD-1 peptide sequence of Table 11;

ii) encodes a plurality of antigenic peptide sequences of Table 11;

iii) exhibits identity over at least 25 nucleotides to a natural cDNA encoding said MD-1 segment;

iv) is a hybridization probe for a gene encoding said Dub11 polypeptide;

E) said primate MD-2:

a) polypeptide is from a human; or

b) nucleic acid:

i) encodes an antigenic MD-2 peptide sequence of Table 11;

ii) encodes a plurality of antigenic peptide sequences of Table 11;

iii) exhibits identity over at least 25 nucleotides to a natural cDNA encoding said MD-2 segment;

iv) is a hybridization probe for a gene encoding said primate MD-2 polypeptide; or

F) said rodent MD-2:

a) polypeptide is from a mouse; or

b) nucleic acid:

i) encodes an antigenic MD-2 peptide sequence of Table 11;

ii) encodes a plurality of antigenic peptide sequences of Table 11;

iii) exhibits identity over at least 25 nucleotides to a natural cDNA encoding said MD-2 segment; or

iv) is a hybridization probe for a gene encoding said rodent MD-2 polypeptide.

57. The nucleic acid of Claim 56, which:

a) is an expression vector;

b) further comprises an origin of replication;

c) is from a natural source;

d) comprises a detectable label;

e) comprises synthetic nucleotide sequence;

f) is less than 6 kb, preferably less than 3 kb;

g) is from a primate, including a human;

h) comprises a natural full length coding sequence; or
i) is a PCR primer, PCR product, or mutagenesis primer.

58. A cell or tissue comprising a recombinant nucleic acid of Claim 56, including wherein said cell is:
a) a prokaryotic cell;
b) a eukaryotic cell;
c) a bacterial cell;
d) a yeast cell;
e) an insect cell;
f) a mammalian cell;
g) a mouse cell;
h) a primate cell; or
i) a human cell.

59. A kit comprising said nucleic acid of Claim 56, and:
a) a compartment comprising said nucleic acid;
b) a compartment comprising a nucleic acid encoding another chemokine, including HCC1, HCC2, HCC3, and HCC4; or
c) instructions for use or disposal of reagents in said kit.

60. A nucleic acid which:
a) hybridizes under wash conditions of 45° C and less than 2M salt to the polypeptide coding portion of SEQ ID NO: 24;
b) hybridizes under wash conditions of 45° C and less than 2M salt to the polypeptide coding portions of SEQ ID NO: 31 or 33;
c) hybridizes under wash conditions of 45° C and less than 2M salt to the coding portions of SEQ ID NO: 35 or 37;
d) hybridizes under wash conditions of 45° C and less than 2M salt to the coding portion of SEQ ID NO: 41;
e) hybridizes under wash conditions of 45° C and less than 2M salt to the coding portion of SEQ ID NO: 43 or 45. or
f) hybridizes under wash conditions of 45° C and less than 2M salt to the coding portion of SEQ ID NO: 47.

61. The nucleic acid of Claim 57, wherein:

a) said wash conditions are at 55° C and/or 500 mM salt; or

b) said wash conditions are at 65° C and/or 150 mM salt.

62. A method of modulating physiology or development of a cell or tissue culture cells comprising exposing said cell to an agonist or antagonist of HCC5, primate MD-1, primate MD-2, or rodent MD-2.

63. A method of detecting specific binding to a compound, comprising:

a) contacting said compound to a composition selected from the group of:

i) an antigen binding site which specifically binds to a HCC5 chemokine;

ii) an antigen binding site which specifically binds to Dub11;

iii) an antigen binding site which specifically binds to Dub12;

iv) an antigen binding site which specifically binds to primate MD-1;

v) an antigen binding site which specifically binds to primate MD-2;

vi) an antigen binding site which specifically binds to rodent MD-2;

vii) an expression vector encoding a HCC5 chemokine or fragment thereof;

viii) an expression vector encoding a Dub11 or fragment thereof;

ix) an expression vector encoding a Dub12 or fragment thereof;

x) an expression vector encoding a primate MD-1 or fragment thereof;

xi) an expression vector encoding a primate MD-2 or fragment thereof;

xii) an expression vector encoding a rodent MD-2 or fragment thereof;

xiii) a substantially pure protein which is specifically recognized by said antigen binding site of (i);

xiv) a substantially pure protein which is specifically recognized by said antigen binding site of (ii);

xiv) a substantially pure protein which is specifically recognized by said antigen binding site of (iii);

xiv) a substantially pure protein which is specifically recognized by said antigen binding site of (iv);

xiv) a substantially pure protein which is specifically recognized by said antigen binding site of (v);

xiv) a substantially pure protein which is specifically recognized by said antigen binding site of (vi);

ix) a substantially pure HCC5 chemokine or peptide thereof of Claim 43, or a fusion protein comprising a 30 amino acid sequence portion of HCC5 chemokine sequence;

x) a substantially pure Dub11 or peptide thereof of Claim 43, or a fusion protein comprising a 30 amino acid sequence portion of Dub11 sequence;

xi) a substantially pure Dub12 or peptide thereof of Claim 43, or a fusion protein comprising a 30 amino acid sequence portion of Dub11 sequence;

xi) a substantially pure primate MD-1 or peptide thereof of Claim 43, or a fusion protein comprising a 30 amino acid sequence portion of primate MD-1 sequence;

xi) a substantially pure primate MD-2 or peptide thereof of Claim 43, or a fusion protein comprising a 30 amino acid sequence portion of primate MD-2 sequence;

xi) a substantially pure rodent MD-2 or peptide thereof of Claim 43, or a fusion protein comprising a 30 amino acid sequence portion of rodent MD-2 sequence; and

b) detecting binding of said compound to said composition.

64. An isolated or recombinant polynucleotide which:

a) encodes at least 17 contiguous amino acid residues of SEQ ID NO: 54;

b) encodes at least two distinct segments of at least 10 contiguous amino acid residues of SEQ ID NO 54; or

c) comprises one or more segments at least 21 contiguous nucleotides of SEQ ID NO: 53.

65. A method of making:

a) a polypeptide comprising expressing an expression vector of Claim 64, thereby producing said polypeptide;

b) a duplex nucleic acid comprising contacting a polynucleotide of Claim 64 with a complementary nucleic acid, thereby resulting in production of said duplex nucleic acid;

c) a synthetic polynucleotide of Claim 64, comprising chemically polymerizing nucleotides to produce said polynucleotide; or

d) a polynucleotide of Claim 64 comprising using a PCR method.

66. An isolated or recombinant antigenic polypeptide comprising at least:

a) one segment comprising at least 17 contiguous amino acids from SEQ ID NO: 54; or

b) at least two distinct segments of at least 11 contiguous amino acids from SEQ ID NO: 54.

67. The antigenic polypeptide of Claim 66, comprising at least one segment comprising at least 17 contiguous amino acids from SEQ ID NO: 54.

68. The polypeptide of Claim 66, which exhibits at least two non-overlapping epitopes which are selective for primate protein of SEQ ID NO: 54.

69. The polypeptide of Claim 66, wherein said polypeptide:

a) is a 5-fold or less substitution from a natural sequence; or

b) is a deletion or insertion variant from a natural sequence.

70. A kit comprising said polypeptide of Claim 66, and instructions for the use or disposal of said polypeptide or other reagents of said kit.

71. The antigenic polypeptide of Claim 66, comprising at least two distinct segments of at least 11 contiguous amino acids from SEQ ID NO: 54.

72. The polypeptide of Claim 71:

a) which comprises at least one sequence from (SEQ ID NO: 54) KESRYVHD (residues 120-127), DKHFEVLH (residues 127-134), HSDLEPQM (residues 134-141), QKDINKNM (residues 177-184), YAPKLQEF (residues 203-210), SEEDILRM (residues 219-226), LRMELIIL (residues 224-231), ELCPVTII (residues 237-244), and LFLQVDAL (residues 249-256); and/or

b) wherein said segments of at least 11 contiguous amino acids comprise one said segment with at least 14 contiguous amino acids from SEQ ID NO: 54.

73. The polypeptide of Claim 71, which exhibits at least two non-overlapping epitopes which are selective for primate protein of SEQ ID NO: 54.

74. The polypeptide of Claim 71, wherein said polypeptide:

a) comprises a mature sequence of SEQ ID NO: 2;

b) binds with selectivity to an antibody generated against an immunogen of SEQ ID NO: 54;

c) comprises a plurality of polypeptide segments of 17 contiguous amino acids of SEQ ID NO: 54; or

d) is a natural allelic variant of SEQ ID NO: 54.

75. The polypeptide of Claim 71, wherein said polypeptide:

a) is in a sterile composition;

b) has a length at least 30 amino acids;
c) is not glycosylated;
d) is denatured;
e) is a synthetic polypeptide;
f) is attached to a solid substrate; or
g) is a fusion protein with a detection or purification tag, including a FLAG, His6, or Ig sequence.

76. The polypeptide of Claim 71, wherein said polypeptide:
a) is a 5-fold or less substitution from a natural sequence; or
b) is a deletion or insertion variant from a natural sequence.

77. A kit comprising said polypeptide of Claim 71, and instructions for the use or disposal of said polypeptide or other reagents of said kit.

78. A method using said polypeptide of Claim 71:
a) to label said polypeptide, comprising labeling said polypeptide with a radioactive label;
b) to separate said polypeptide from another polypeptide in a mixture, comprising running said mixture on a chromatography matrix, thereby separating said polypeptides;
c) to identify a compound that binds selectively to said polypeptide, comprising incubating said compound with said polypeptide under appropriate conditions; thereby causing said component to bind to said polypeptide; or
d) to conjugate said polypeptide to a matrix, comprising derivatizing said polypeptide with a reactive reagent, and conjugating said polypeptide to said matrix; or
e) inducing an antibody response to said polypeptide, comprising introducing said polypeptide as an antigen to an immune system, thereby inducing said response.

79. A binding compound comprising an antigen binding portion from an antibody which binds with selectivity to a polypeptide of Claim 66.

80. A method of evaluating the selectivity of binding of a compound to cyclin E2, comprising contacting said compound to a recombinant cyclin E2 polypeptide and at least one other cyclin; and comparing binding of said compound to said cyclins.

81. The polypeptide of Claim 67:

a) which comprises at least one sequence from (SEQ ID NO: 54) KESRYVHD (residues 120-127), DKHFEVLH (residues 127-134), HSDLEPQM (residues 134-141), QKDINKNM (residues 177-184), YAPKLQEF (residues 203-210), SEEDILRM (residues 219-226), LRMELIIL (residues 224-231), ELCPVTII (residues 237-244), and LFLQVDAL (residues 249-256); and/or

b) wherein said segment comprising at least 17 contiguous amino acids exhibits at least 23 contiguous amino acids from SEQ ID NO: 54.

82. The polypeptide of Claim 67, wherein said polypeptide:

a) comprises a mature sequence of SEQ ID NO: 54;

b) binds with selectivity to an antibody generated against an immunogen of SEQ ID NO: 54;

c) comprises a plurality of polypeptide segments comprising at least 17 contiguous amino acids of SEQ ID NO: 54; or

d) is a natural allelic variant of SEQ ID NO: 54.

83. The polypeptide of Claim 67, wherein said polypeptide:

a) is in a sterile composition;

b) has a length at least 30 amino acids;

c) is not glycosylated;

d) is denatured;

e) is a synthetic polypeptide;

f) is attached to a solid substrate; or

g) is a fusion protein with a detection or purification tag, including a FLAG, His6, or Ig sequence.

84. A method using said polypeptide of Claim 67:

a) to label said polypeptide, comprising labeling said polypeptide with a radioactive label;

b) to separate said polypeptide from another polypeptide in a mixture, comprising running said mixture on a chromatography matrix, thereby separating said polypeptides;

c) to identify a compound that binds selectively to said polypeptide, comprising incubating said compound with said polypeptide under appropriate conditions; thereby causing said component to bind to said polypeptide;

d) to conjugate said polypeptide to a matrix, comprising derivatizing said polypeptide with a reactive reagent, and conjugating said polypeptide to said matrix; or

e) inducing an antibody response to said polypeptide, comprising introducing said polypeptide as an antigen to an immune system, thereby inducing said response.

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 65                  70                  75                  80

Gly Leu Ser Ser Gln Thr Ser Gly Leu Leu Ala Ser Phe Asn Glu Val
                 85                  90                  95

Gly Asn Thr Ala Leu Ile Val Phe Val Ser Tyr Phe Gly Ser Arg Val
            100                 105                 110

His Arg Pro Arg Met Ile Gly Tyr Gly Ala Ile Leu Val Ala Leu Ala
        115                 120                 125
```

```
Gly Leu Leu Met Thr Leu Pro His Phe Ile Ser Glu Pro Tyr Arg Tyr
    130                 135                 140

Asp Asn Thr Ser Pro Glu Asp Met Pro Gln Asp Phe Lys Ala Ser Leu
145                 150                 155                 160

Cys Leu Pro Thr Thr Ser Ala Pro Ala Ser Ala Pro Ser Asn Gly Asn
                165                 170                 175

Cys Ser Ser Tyr Thr Glu Thr Gln His Leu Ser Val Val Gly Ile Met
            180                 185                 190

Phe Val Ala Gln Thr Leu Leu Gly Val Gly Gly Val Pro Ile Gln Pro
        195                 200                 205

Phe Gly Ile Ser Tyr Ile Asp Asp Phe Ala His Asn Ser Asn Ser Pro
    210                 215                 220

Leu Tyr Leu Gly Ile Leu Phe Ala Val Thr Met Met Gly Pro Gly Leu
225                 230                 235                 240

Ala Phe Gly Leu Gly Ser Leu Met Leu Arg Leu Tyr Val Asp Ile Asn
                245                 250                 255

Gln Met Pro Glu Gly Gly Ile Ser Leu Thr Ile Lys Asp Pro Arg Trp
            260                 265                 270

Val Gly Ala Trp Trp Leu Gly Phe Leu Ile Ala Ala Gly Ala Val Ala
        275                 280                 285

Leu Ala Ala Ile Pro Tyr Phe Phe Phe Pro Lys Glu Met Pro Lys Glu
    290                 295                 300

Lys Arg Glu Leu Gln Phe Arg Arg Lys Val Leu Ala Val Thr Asp Ser
305                 310                 315                 320

Pro Ala Arg Lys Gly Lys Asp Ser Pro Ser Lys Gln Ser Pro Gly Glu
                325                 330                 335

Ser Thr Lys Lys Gln Asp Gly Leu Val Gln Ile Ala Pro Asn Leu Thr
            340                 345                 350

Val Ile Gln Phe Ile Lys Val Phe Pro Arg Val Leu Leu Gln Thr Leu
        355                 360                 365

Arg His Pro Ile Phe Leu Leu Val Val Leu Ser Gln Val Cys Leu Ser
    370                 375                 380

Ser Met Ala Ala Gly Met Ala Thr Phe Leu Pro Lys Phe Leu Glu Arg
385                 390                 395                 400

Gln Phe Ser Ile Thr Ala Ser Tyr Ala Asn Leu Leu Ile Gly Cys Leu
                405                 410                 415

Ser Phe Pro Ser Val Ile Val Gly Ile Val Val Gly Gly Val Leu Val
            420                 425                 430

Lys Arg Leu His Leu Gly Pro Val Gly Cys Gly Ala Leu Cys Leu Leu
        435                 440                 445
```

Gly Met Leu Leu Cys Leu Phe Phe Ser Leu Pro Leu Phe Phe Ile Gly
450 455 460

Cys Ser Ser His Gln Ile Ala Gly Ile Thr His Gln Thr Ser Ala His
465 470 475 480

Pro Gly Leu Glu Leu Ser Pro Ser Cys Met Glu Ala Cys Ser Cys Pro
485 490 495

Leu Asp Gly Phe Asn Pro Val Cys Asp Pro Ser Thr Arg Val Glu Tyr
500 505 510

Ile Thr Pro Cys His Ala Gly Cys Ser Ser Trp Val Val Gln Asp Ala
515 520 525

Leu Asp Asn Ser Gln Val Phe Tyr Thr Asn Cys Ser Cys Val Val Glu
530 535 540

Gly Asn Pro Val Leu Ala Gly Ser Cys Asp Ser Thr Cys Ser His Leu
545 550 555 560

Val Val Pro Phe Leu Leu Leu Val Ser Leu Gly Ser Ala Leu Ala Cys
565 570 575

Leu Thr His Thr Pro Ser Phe Met Leu Ile Leu Arg Gly Val Lys Lys
580 585 590

Glu Asp Lys Thr Leu Ala Val Gly Ile Gln Phe Met Phe Leu Arg Ile
595 600 605

Leu Ala Trp Met Pro Ser Pro Val Ile His Gly Ser Ala Ile Asp Thr
610 615 620

Thr Cys Val His Trp Ala Leu Ser Cys Gly Arg Arg Ala Val Cys Arg
625 630 635 640

Tyr Tyr Asn Asn Asp Leu Leu Arg Asn Arg Phe Ile Gly Leu Gln Phe
645 650 655

Phe Phe Lys Thr Gly Ser Val Ile Cys Phe Ala Leu Val Leu Ala Val
660 665 670

Leu Arg Gln Gln Asp Lys Glu Ala Arg Thr Lys Glu Ser Arg Ser Ser
675 680 685

Pro Ala Val Glu Gln Gln Leu Leu Val Ser Gly Pro Gly Lys Lys Pro
690 695 700

Glu Asp Ser Arg Val
705

<210> 3
<211> 643
<212> PRT
<213> Unknown

<220>
<223> Description of Unknown Organism:primate

<400> 3

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Met Gly Leu Leu Pro Lys Leu Gly Val Ser Gln Gly Ser Asp Thr Ser
 1               5                  10                  15

Thr Ser Arg Ala Gly Arg Cys Ala Arg Ser Val Phe Gly Asn Ile Lys
            20                  25                  30

Val Phe Val Leu Cys Gln Gly Leu Leu Gln Leu Cys Gln Leu Leu Tyr
        35                  40                  45

Ser Ala Tyr Phe Lys Ser Ser Leu Thr Thr Ile Glu Lys Arg Phe Gly
    50                  55                  60

Leu Ser Ser Ser Ser Ser Gly Leu Ile Ser Ser Leu Asn Glu Ile Ser
65                  70                  75                  80

Asn Ala Ile Leu Ile Ile Phe Val Ser Tyr Phe Gly Ser Arg Val His
                85                  90                  95

Arg Pro Arg Leu Ile Gly Ile Gly Gly Leu Phe Leu Ala Ala Gly Ala
            100                 105                 110

Phe Ile Leu Thr Leu Pro His Phe Leu Ser Glu Pro Tyr Gln Tyr Thr
        115                 120                 125

Leu Ala Ser Thr Gly Asn Asn Ser Arg Leu Gln Ala Glu Leu Cys Gln
    130                 135                 140

Lys His Trp Gln Asp Leu Pro Pro Ser Lys Cys His Ser Thr Thr Gln
145                 150                 155                 160

Asn Pro Gln Lys Glu Thr Ser Ser Met Trp Gly Leu Met Val Val Ala
                165                 170                 175

Gln Leu Leu Ala Gly Ile Gly Thr Val Pro Ile Gln Pro Phe Gly Ile
            180                 185                 190

Ser Tyr Val Asp Asp Phe Ser Glu Pro Ser Asn Ser Pro Leu Tyr Ile
        195                 200                 205

Ser Ile Leu Phe Ala Ile Ser Val Phe Gly Pro Ala Phe Gly Tyr Leu
    210                 215                 220

Leu Gly Ser Ile Met Leu Gln Ile Phe Val Asp Tyr Gly Arg Val Asn
225                 230                 235                 240

Thr Ala Ala Val Asn Leu Val Pro Gly Asp Pro Arg Trp Ile Gly Ala
                245                 250                 255

Trp Trp Leu Gly Leu Leu Ile Ser Ser Ala Leu Leu Val Leu Thr Ser
            260                 265                 270

Phe Pro Phe Phe Phe Phe Pro Arg Ala Met Pro Ile Gly Ala Lys Arg
        275                 280                 285

Ala Pro Ala Thr Ala Asp Glu Ala Arg Lys Leu Glu Glu Ala Lys Ser
    290                 295                 300

Arg Gly Ser Leu Val Asp Phe Ile Lys Arg Phe Pro Cys Ile Phe Leu
305                 310                 315                 320
```

Arg Leu Leu Met Asn Ser Leu Phe Val Leu Val Val Leu Ala Gln Cys
325 330 335

Thr Phe Ser Ser Val Ile Ala Gly Leu Ser Thr Phe Leu Asn Lys Phe
340 345 350

Leu Glu Lys Gln Tyr Gly Thr Ser Ala Ala Tyr Ala Asn Phe Leu Ile
355 360 365

Gly Ala Val Asn Leu Pro Ala Ala Ala Leu Gly Met Leu Phe Gly Gly
370 375 380

Ile Leu Met Lys Arg Phe Val Phe Ser Leu Gln Thr Ile Pro Arg Ile
385 390 395 400

Ala Thr Thr Ile Ile Thr Ile Ser Met Ile Leu Cys Val Pro Leu Phe
405 410 415

Phe Met Gly Cys Ser Thr Pro Thr Val Ala Glu Val Tyr Pro Pro Ser
420 425 430

Thr Ser Ser Ser Ile His Pro Gln Ser Pro Ala Cys Arg Arg Asp Cys
435 440 445

Ser Cys Pro Asp Ser Ile Phe His Pro Val Cys Gly Asp Asn Gly Ile
450 455 460

Glu Tyr Leu Ser Pro Cys His Ala Gly Cys Ser Asn Ile Asn Met Ser
465 470 475 480

Ser Ala Thr Ser Lys Gln Leu Ile Tyr Leu Asn Cys Ser Cys Val Thr
485 490 495

Gly Gly Ser Ala Ser Ala Lys Thr Gly Ser Cys Pro Val Pro Cys Ala
500 505 510

His Phe Leu Leu Pro Ala Ile Phe Leu Ile Ser Phe Val Ser Leu Ile
515 520 525

Ala Cys Ile Ser His Asn Pro Leu Tyr Met Met Val Leu Arg Val Val
530 535 540

Asn Gln Glu Glu Lys Ser Phe Ala Ile Gly Val Gln Phe Leu Leu Met
545 550 555 560

Arg Leu Leu Ala Trp Leu Pro Ser Pro Ala Leu Tyr Gly Leu Thr Ile
565 570 575

Asp His Ser Cys Ile Arg Trp Asn Ser Leu Cys Leu Gly Arg Arg Gly
580 585 590

Ala Cys Ala Tyr Tyr Asp Asn Asp Ala Leu Arg Asp Arg Tyr Leu Gly
595 600 605

Leu Gln Met Gly Tyr Lys Ala Leu Gly Met Leu Leu Leu Cys Phe Ile
610 615 620

Ser Trp Arg Val Lys Lys Asn Lys Glu Tyr Asn Val Gln Lys Ala Ala
625 630 635 640

Gly Leu Ile

<210> 4
<211> 643
<212> PRT
<213> Unknown

<220>
<223> Description of Unknown Organism:rodent

<400> 4

```
Met Gly Leu Leu Leu Lys Pro Gly Ala Arg Gln Gly Ser Gly Thr Ser
 1               5                  10                  15

Ser Val Pro Asp Arg Arg Cys Pro Arg Ser Val Phe Ser Asn Ile Lys
            20                  25                  30

Val Phe Val Leu Cys His Gly Leu Leu Gln Leu Cys Gln Leu Leu Tyr
        35                  40                  45

Ser Ala Tyr Phe Lys Ser Ser Leu Thr Thr Ile Glu Lys Arg Phe Gly
    50                  55                  60

Leu Ser Ser Ser Ser Ser Gly Leu Ile Ser Ser Leu Asn Glu Ile Ser
65                  70                  75                  80

Asn Ala Thr Leu Ile Ile Phe Ile Ser Tyr Phe Gly Ser Arg Val Asn
                85                  90                  95

Arg Pro Arg Met Ile Gly Ile Gly Gly Leu Leu Leu Ala Ala Gly Ala
            100                 105                 110

Phe Val Leu Thr Leu Pro His Phe Leu Ser Glu Pro Tyr Gln Tyr Thr
        115                 120                 125

Ser Thr Thr Asp Gly Asn Arg Ser Ser Phe Gln Thr Asp Leu Cys Gln
    130                 135                 140

Lys His Phe Gly Ala Leu Pro Pro Ser Lys Cys His Ser Thr Val Pro
145                 150                 155                 160

Asp Thr His Lys Glu Thr Ser Ser Leu Trp Gly Leu Met Val Val Ala
                165                 170                 175

Gln Leu Leu Ala Gly Ile Gly Thr Val Pro Ile Gln Pro Phe Gly Ile
            180                 185                 190

Ser Tyr Val Asp Asp Phe Ala Glu Pro Thr Asn Ser Pro Leu Tyr Ile
        195                 200                 205

Ser Ile Leu Phe Ala Ile Ala Val Phe Gly Pro Ala Phe Gly Tyr Leu
    210                 215                 220

Leu Gly Ser Val Met Leu Arg Ile Phe Val Asp Tyr Gly Arg Val Asp
225                 230                 235                 240

Thr Ala Thr Val Asn Leu Ser Pro Gly Asp Pro Arg Trp Ile Gly Ala
                245                 250                 255

Trp Trp Leu Gly Leu Leu Ile Ser Ser Gly Phe Leu Ile Val Thr Ser
            260                 265                 270
```

```
Leu Pro Phe Phe Phe Phe Pro Arg Ala Met Ser Arg Gly Ala Glu Arg
        275                 280                 285

Ser Val Thr Ala Glu Glu Thr Met Gln Thr Glu Glu Asp Lys Ser Arg
    290                 295                 300

Gly Ser Leu Met Asp Phe Ile Lys Arg Phe Pro Arg Ile Phe Leu Arg
305                 310                 315                 320

Leu Leu Met Asn Pro Leu Phe Met Leu Val Val Leu Ser Gln Cys Thr
                325                 330                 335

Phe Ser Ser Val Ile Ala Gly Leu Ser Thr Phe Leu Asn Lys Phe Leu
            340                 345                 350

Glu Lys Gln Tyr Gly Ala Thr Ala Ala Tyr Ala Asn Phe Leu Ile Gly
        355                 360                 365

Ala Val Asn Leu Pro Ala Ala Ala Leu Gly Met Leu Phe Gly Gly Ile
    370                 375                 380

Leu Met Lys Arg Phe Val Phe Pro Leu Gln Thr Ile Pro Arg Val Ala
385                 390                 395                 400

Ala Thr Ile Ile Thr Ile Ser Met Ile Leu Cys Val Pro Leu Phe Phe
                405                 410                 415

Met Gly Cys Ser Thr Ser Ala Val Ala Glu Val Tyr Pro Pro Ser Thr
            420                 425                 430

Ser Ser Ser Ile His Pro Gln Gln Pro Pro Ala Cys Arg Arg Asp Cys
        435                 440                 445

Ser Cys Pro Asp Ser Phe Phe His Pro Val Cys Gly Asp Asn Gly Val
    450                 455                 460

Glu Tyr Val Ser Pro Cys His Ala Gly Cys Ser Ser Thr Asn Thr Ser
465                 470                 475                 480

Ser Glu Ala Ser Lys Glu Pro Ile Tyr Leu Asn Cys Ser Cys Val Ser
                485                 490                 495

Gly Gly Ser Ala Ser Gln Asp Arg Leu Met Pro His Val Leu Arg Ala
            500                 505                 510

Leu Leu Leu Pro Ser Ile Phe Leu Ile Ser Phe Ala Ala Leu Ile Ala
        515                 520                 525

Cys Ile Ser His Asn Pro Leu Tyr Met Met Val Leu Arg Val Val Asn
    530                 535                 540

Gln Asp Glu Lys Ser Phe Ala Ile Gly Val Gln Phe Leu Leu Met Arg
545                 550                 555                 560

Leu Leu Ala Trp Leu Pro Ala Pro Ser Leu Tyr Gly Leu Leu Ile Asp
                565                 570                 575

Ser Ser Cys Val Arg Trp Asn Tyr Leu Cys Ser Gly Arg Arg Gly Ala
            580                 585                 590
```

Cys Ala Tyr Tyr Asp Asn Asp Ala Leu Arg Asn Arg Tyr Leu Gly Leu
595 600 605

Gln Met Val Tyr Lys Ala Leu Gly Thr Leu Leu Leu Phe Phe Ile Ser
610 615 620

Trp Arg Met Lys Lys Asn Arg Glu Tyr Ser Leu Gln Glu Asn Thr Ser
625 630 635 640

Gly Leu Ile

<210> 5
<211> 1137
<212> DNA
<213> Unknown

<220>
<221> CDS
<222> (99)..(998)

<220>
<221> misc_difference
<222> (367)
<223> may be A; translation would be Asn

<220>
<223> Description of Unknown Organism:primate

<400> 5
cgcaggcgga ccgggggcaa aggaggtggc atgtcggtca ggcacagcag ggtcctgtgt 60

ccgcgctgag ccgcgctctc cctgctccag caaggacc atg agg gcg ctg gag ggg 116
Met Arg Ala Leu Glu Gly
1 5

cca ggc ctg tcg ctg ctg tgc ctg gtg ttg gcg ctg cct gcc ctg ctg 164
Pro Gly Leu Ser Leu Leu Cys Leu Val Leu Ala Leu Pro Ala Leu Leu
10 15 20

ccg gtg ccg gct gta cgc gga gtg gca gaa aca ccc acc tac ccc tgg 212
Pro Val Pro Ala Val Arg Gly Val Ala Glu Thr Pro Thr Tyr Pro Trp
25 30 35

cgg gac gca gag aca ggg gag cgg ctg gtg tgc gcc cag tgc ccc cca 260
Arg Asp Ala Glu Thr Gly Glu Arg Leu Val Cys Ala Gln Cys Pro Pro
40 45 50

ggc acc ttt gtg cag cgg ccg tgc cgc cga gac agc ccc atg acg tgt 308
Gly Thr Phe Val Gln Arg Pro Cys Arg Arg Asp Ser Pro Met Thr Cys
55 60 65 70

ggc ccg tgt cca ccg cgc cac tac acg cag ttc tgg aac tac ctg gag 356
Gly Pro Cys Pro Pro Arg His Tyr Thr Gln Phe Trp Asn Tyr Leu Glu
75 80 85

cgc tgc cgc tac tgc tac gtc ctc tgc ggg gag cgt gag gag gag gca 404
Arg Cys Arg Tyr Cys Tyr Val Leu Cys Gly Glu Arg Glu Glu Glu Ala
90 95 100

```
cgg gct tgc cac gcc acc cac aac cgt gcc tgc cgc tgc cgc acc ggc   452
Arg Ala Cys His Ala Thr His Asn Arg Ala Cys Arg Cys Arg Thr Gly
        105                 110                 115

ttc ttc gcg cac gct ggt ttc tgc ttg gag cac gca tcg tgt cca cct   500
Phe Phe Ala His Ala Gly Phe Cys Leu Glu His Ala Ser Cys Pro Pro
    120                 125                 130

ggt gcc ggc gtg att gcc ccg ggc acc ccc agc cag aac acg cag tgc   548
Gly Ala Gly Val Ile Ala Pro Gly Thr Pro Ser Gln Asn Thr Gln Cys
135                 140                 145                 150

cag ccg tgc ccc cca ggc acc ttc tca gcc agc agc tcc agc tca gag   596
Gln Pro Cys Pro Pro Gly Thr Phe Ser Ala Ser Ser Ser Ser Ser Glu
                155                 160                 165

cag tgc cag ccc cac cgc aac tgc acg gcc ctg ggc ctg gcc ctc aat   644
Gln Cys Gln Pro His Arg Asn Cys Thr Ala Leu Gly Leu Ala Leu Asn
            170                 175                 180

gtg cca ggc tct tcc tcc cat gac acc ctg tgc acc agc tgc act ggc   692
Val Pro Gly Ser Ser Ser His Asp Thr Leu Cys Thr Ser Cys Thr Gly
        185                 190                 195

ttc ccc ctc agc acc agg gta cca gga gct gag gag tgt gag cgt gcc   740
Phe Pro Leu Ser Thr Arg Val Pro Gly Ala Glu Glu Cys Glu Arg Ala
    200                 205                 210

gtc atc gac ttt gtg gct ttc cag gac atc tcc atc aag agg ctg cag   788
Val Ile Asp Phe Val Ala Phe Gln Asp Ile Ser Ile Lys Arg Leu Gln
215                 220                 225                 230

cgg ctg ctg cag gcc ctc gag gcc ccg gag ggc tgg ggt ccg aca cca   836
Arg Leu Leu Gln Ala Leu Glu Ala Pro Glu Gly Trp Gly Pro Thr Pro
                235                 240                 245

agg gcg ggc cgc gcg gcc ttg cag ctg aag ctg cgt cgg cgg ctc acg   884
Arg Ala Gly Arg Ala Ala Leu Gln Leu Lys Leu Arg Arg Arg Leu Thr
            250                 255                 260

gag ctc ctg ggg gcg cag gac ggg gcg ctg ctg gtg cgg ctg ctg cag   932
Glu Leu Leu Gly Ala Gln Asp Gly Ala Leu Leu Val Arg Leu Leu Gln
        265                 270                 275

gcg ctg cgc gtg gcc agg atg ccc ggg ctg gag cgg agc gtc cgt gag   980
Ala Leu Arg Val Ala Arg Met Pro Gly Leu Glu Arg Ser Val Arg Glu
    280                 285                 290

cgc ttc ctc cct gtg cac tgatcctggc cccctcttat ttattctaca         1028
Arg Phe Leu Pro Val His
295                 300

tccttggcac cccacttgca ctgaaagagg ctttttttta aatagaagaa atgaggtttc 1088

ttaaagctta tttttataaa gctttttcat aaaaaaaaaa aaaaaaaaa             1137
```

<210> 6
<211> 300
<212> PRT

<213> Unknown

<400> 6

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Met Arg Ala Leu Glu Gly Pro Gly Leu Ser Leu Leu Cys Leu Val Leu
  1               5                  10                  15

Ala Leu Pro Ala Leu Leu Pro Val Pro Ala Val Arg Gly Val Ala Glu
             20                  25                  30

Thr Pro Thr Tyr Pro Trp Arg Asp Ala Glu Thr Gly Glu Arg Leu Val
         35                  40                  45

Cys Ala Gln Cys Pro Pro Gly Thr Phe Val Gln Arg Pro Cys Arg Arg
     50                  55                  60

Asp Ser Pro Met Thr Cys Gly Pro Cys Pro Pro Arg His Tyr Thr Gln
 65                  70                  75                  80

Phe Trp Asn Tyr Leu Glu Arg Cys Arg Tyr Cys Tyr Val Leu Cys Gly
                 85                  90                  95

Glu Arg Glu Glu Glu Ala Arg Ala Cys His Ala Thr His Asn Arg Ala
            100                 105                 110

Cys Arg Cys Arg Thr Gly Phe Phe Ala His Ala Gly Phe Cys Leu Glu
        115                 120                 125

His Ala Ser Cys Pro Pro Gly Ala Gly Val Ile Ala Pro Gly Thr Pro
    130                 135                 140

Ser Gln Asn Thr Gln Cys Gln Pro Cys Pro Pro Gly Thr Phe Ser Ala
145                 150                 155                 160

Ser Ser Ser Ser Ser Glu Gln Cys Gln Pro His Arg Asn Cys Thr Ala
                165                 170                 175

Leu Gly Leu Ala Leu Asn Val Pro Gly Ser Ser Ser His Asp Thr Leu
            180                 185                 190

Cys Thr Ser Cys Thr Gly Phe Pro Leu Ser Thr Arg Val Pro Gly Ala
        195                 200                 205

Glu Glu Cys Glu Arg Ala Val Ile Asp Phe Val Ala Phe Gln Asp Ile
    210                 215                 220

Ser Ile Lys Arg Leu Gln Arg Leu Leu Gln Ala Leu Glu Ala Pro Glu
225                 230                 235                 240

Gly Trp Gly Pro Thr Pro Arg Ala Gly Arg Ala Ala Leu Gln Leu Lys
                245                 250                 255

Leu Arg Arg Arg Leu Thr Glu Leu Leu Gly Ala Gln Asp Gly Ala Leu
            260                 265                 270

Leu Val Arg Leu Leu Gln Ala Leu Arg Val Ala Arg Met Pro Gly Leu
        275                 280                 285

Glu Arg Ser Val Arg Glu Arg Phe Leu Pro Val His
    290                 295                 300
```

<210> 7
<211> 1031
<212> DNA
<213> Unknown

<220>
<221> CDS
<222> (402)..(1031)

<220>
<223> Description of Unknown Organism:primate

<400> 7
ccgactcant ccctcgccga ccagtctggg cagcggagga gggtggttgg cagtggctgg 60

aagcttcgct atgggaagtc gttcctttgc tctctcgcgc ccagtcctcc tccctggttc 120

tcctcagccg ctgtcggagg agagcacccg gagacgcggg ctgcagtcgc ggcggcttct 180

ccccgcctgg gcggccgcgc cgctgggcag gtgctgagcg cccctagagc ctcccttgcc 240

gcctccctcc tctgcccggc cgcagcagtg cacatggggt gttggaggta gatgggctcc 300

cggcccggga ggcggcggtg gatgcggcgc tgggcagaag cagccgccga ttccagctgc 360

cccgcgcgcc ccgggcgccc ctgcgagtcc ccggttcagc c atg ggg acc tct ccg 416
Met Gly Thr Ser Pro
1 5

agc agc agc acc gcc ctc gcc tcc tgc agc cgc atc gcc cgc cga gcc 464
Ser Ser Ser Thr Ala Leu Ala Ser Cys Ser Arg Ile Ala Arg Arg Ala
10 15 20

aca gcc acg atg atc gcg ggc tcc ctt ctc ctg ctt gga ttc ctt agc 512
Thr Ala Thr Met Ile Ala Gly Ser Leu Leu Leu Leu Gly Phe Leu Ser
25 30 35

acc acc aca gct cag cca gaa cag aag gcc tcg aat ctc att ggc aca 560
Thr Thr Thr Ala Gln Pro Glu Gln Lys Ala Ser Asn Leu Ile Gly Thr
40 45 50

tac cgc cat gtt gac cgt gcc acc ggc cag gtg cta acc tgt gac aag 608
Tyr Arg His Val Asp Arg Ala Thr Gly Gln Val Leu Thr Cys Asp Lys
55 60 65

tgt cca gca gga acc tat gtc tct gag cat tgt acc aac aca agc tgc 656
Cys Pro Ala Gly Thr Tyr Val Ser Glu His Cys Thr Asn Thr Ser Cys
70 75 80 85

gcg tct ggc agc agt tgc cct gtg ggg acc ttt acc agg cat gag aat 704
Ala Ser Gly Ser Ser Cys Pro Val Gly Thr Phe Thr Arg His Glu Asn
90 95 100

ggc ata gag aaa tgc cat gac tgt agt cag cca tgc cca tgg cca atg 752
Gly Ile Glu Lys Cys His Asp Cys Ser Gln Pro Cys Pro Trp Pro Met
105 110 115

att gag aaa tta cct tgt gct gcc ttg act gac cga gaa tgc act tgc 800
Ile Glu Lys Leu Pro Cys Ala Ala Leu Thr Asp Arg Glu Cys Thr Cys
120 125 130

```
cca cct ggc atg ttc cag tct aac gct acc tgt gcc ccc cat acg gtg   848
Pro Pro Gly Met Phe Gln Ser Asn Ala Thr Cys Ala Pro His Thr Val
    135                 140                 145

tgt cct gtg ggt tgg ggt gtg cgg aag aaa ggg aca gag act gag gat   896
Cys Pro Val Gly Trp Gly Val Arg Lys Lys Gly Thr Glu Thr Glu Asp
150                 155                 160                 165

gtg cgg tgt aag cag tgt gct cgg ggg tac ttc tca gat gtg cct tct   944
Val Arg Cys Lys Gln Cys Ala Arg Gly Tyr Phe Ser Asp Val Pro Ser
                170                 175                 180

agt gtg atg aac gca aag cat aca cag act gtc tgg atc aga acc tgg   992
Ser Val Met Asn Ala Lys His Thr Gln Thr Val Trp Ile Arg Thr Trp
            185                 190                 195

ttg gtg atc aag ccg ggg gga cca agg aga cag aca act              1031
Leu Val Ile Lys Pro Gly Gly Pro Arg Arg Gln Thr Thr
        200                 205                 210
```

<210> 8
<211> 210
<212> PRT
<213> Unknown

<400> 8

```
Met Gly Thr Ser Pro Ser Ser Ser Thr Ala Leu Ala Ser Cys Ser Arg
  1               5                  10                  15

Ile Ala Arg Arg Ala Thr Ala Thr Met Ile Ala Gly Ser Leu Leu Leu
             20                  25                  30

Leu Gly Phe Leu Ser Thr Thr Thr Ala Gln Pro Glu Gln Lys Ala Ser
         35                  40                  45

Asn Leu Ile Gly Thr Tyr Arg His Val Asp Arg Ala Thr Gly Gln Val
     50                  55                  60

Leu Thr Cys Asp Lys Cys Pro Ala Gly Thr Tyr Val Ser Glu His Cys
 65                  70                  75                  80

Thr Asn Thr Ser Cys Ala Ser Gly Ser Ser Cys Pro Val Gly Thr Phe
                 85                  90                  95

Thr Arg His Glu Asn Gly Ile Glu Lys Cys His Asp Cys Ser Gln Pro
            100                 105                 110

Cys Pro Trp Pro Met Ile Glu Lys Leu Pro Cys Ala Ala Leu Thr Asp
        115                 120                 125

Arg Glu Cys Thr Cys Pro Pro Gly Met Phe Gln Ser Asn Ala Thr Cys
    130                 135                 140

Ala Pro His Thr Val Cys Pro Val Gly Trp Gly Val Arg Lys Lys Gly
145                 150                 155                 160

Thr Glu Thr Glu Asp Val Arg Cys Lys Gln Cys Ala Arg Gly Tyr Phe
                165                 170                 175
```

```
Ser Asp Val Pro Ser Ser Val Met Asn Ala Lys His Thr Gln Thr Val
            180                 185                 190

Trp Ile Arg Thr Trp Leu Val Ile Lys Pro Gly Gly Pro Arg Arg Gln
        195                 200                 205

Thr Thr
    210


<210> 9
<211> 2877
<212> DNA
<213> Unknown

<220>
<221> CDS
<222> (410)..(2374)

<220>
<223> Description of Unknown Organism:primate

<400> 9
ggcacgagcc gactcagtcc ctcgccgacc agtctgggca gcggaggagg gtggttggca 60

gtggctggaa gcttcgctat gggaagtcgt tcctttgctc tctcgcgccc agtcctcctc 120

cctggttctc ctcagccgct gtcggaggag agcacccgga gacgcgggct gcagtcgcgg 180

cggcttctcc ccgcctgggc ggccgcgccg ctgggcaggt gctgagcgcc cctagcgcct 240

cccttgccgc ctccctcctc tgcccggccg cagcagtgca catggggtgt tggaggtaga 300

tgggctcccg gcccgggagg cggcggtgga tgcggcgctg ggcagaagca gccgccgatt 360

ccagctgccc cgcgcgcccc gggcgccccc gcgagtcccc ggttcagcc atg ggg acc 418
                                                    Met Gly Thr
                                                      1

tct ccg agc agc agc acc gcc ctc gcc tcc tgc agc cgc atc gcc cgc   466
Ser Pro Ser Ser Ser Thr Ala Leu Ala Ser Cys Ser Arg Ile Ala Arg
  5                  10                  15

cga gcc aca gcc acg atg atc gcg ggc tcc ctt ctc ctg ctt gga ttc • 514
Arg Ala Thr Ala Thr Met Ile Ala Gly Ser Leu Leu Leu Leu Gly Phe
 20                  25                  30                  35

ctt agc acc acc aca gct cag cca gaa cag aag gcc tcg aat ctc att   562
Leu Ser Thr Thr Thr Ala Gln Pro Glu Gln Lys Ala Ser Asn Leu Ile
                 40                  45                  50

ggc aca tac cgc cat gtt gac cgt gcc acc ggc cag gtg cta acc tgt   610
Gly Thr Tyr Arg His Val Asp Arg Ala Thr Gly Gln Val Leu Thr Cys
             55                  60                  65

gac aag tgt cca gca gga acc tat gtc tct gag cat tgt acc aac aca   658
Asp Lys Cys Pro Ala Gly Thr Tyr Val Ser Glu His Cys Thr Asn Thr
         70                  75                  80
```

```
agc ctg cgc gtc tgc agc agt tgc cct gtg ggg acc ttt acc agg cat   706
Ser Leu Arg Val Cys Ser Ser Cys Pro Val Gly Thr Phe Thr Arg His
     85                  90                  95

gag aat ggc ata gag aaa tgc cat gac tgt agt cag cca tgc cca tgg   754
Glu Asn Gly Ile Glu Lys Cys His Asp Cys Ser Gln Pro Cys Pro Trp
100                 105                 110                 115

cca atg att gag aaa tta cct tgt gct gcc ttg act gac cga gaa tgc   802
Pro Met Ile Glu Lys Leu Pro Cys Ala Ala Leu Thr Asp Arg Glu Cys
                120                 125                 130

act tgc cca cct ggc atg ttc cag tct aac gct acc tgt gcc ccc cat   850
Thr Cys Pro Pro Gly Met Phe Gln Ser Asn Ala Thr Cys Ala Pro His
            135                 140                 145

acg gtg tgt cct gtg ggt tgg ggt gtg cgg aag aaa ggg aca gag act   898
Thr Val Cys Pro Val Gly Trp Gly Val Arg Lys Lys Gly Thr Glu Thr
        150                 155                 160

gag gat gtg cgg tgt aag cag tgt gct cgg ggt acc ttc tca gat gtg   946
Glu Asp Val Arg Cys Lys Gln Cys Ala Arg Gly Thr Phe Ser Asp Val
    165                 170                 175

cct tct agt gtg atg aaa tgc aaa gca tac aca gac tgt ctg agt cag   994
Pro Ser Ser Val Met Lys Cys Lys Ala Tyr Thr Asp Cys Leu Ser Gln
180                 185                 190                 195

aac ctg gtg gtg atc aag ccg ggg acc aag gag aca gac aac gtc tgt   1042
Asn Leu Val Val Ile Lys Pro Gly Thr Lys Glu Thr Asp Asn Val Cys
                200                 205                 210

ggc aca ctc ccg tcc ttc tcc agc tcc acc tca cct tcc cct ggc aca   1090
Gly Thr Leu Pro Ser Phe Ser Ser Ser Thr Ser Pro Ser Pro Gly Thr
            215                 220                 225

gcc atc ttt cca cgc cct gag cac atg gaa acc cat gaa gtc cct tcc   1138
Ala Ile Phe Pro Arg Pro Glu His Met Glu Thr His Glu Val Pro Ser
        230                 235                 240

tcc act tat gtt ccc aaa ggc atg aac tca aca gaa tcc aac tct tct   1186
Ser Thr Tyr Val Pro Lys Gly Met Asn Ser Thr Glu Ser Asn Ser Ser
    245                 250                 255

gcc tct gtt aga cca aag gta ctg agt agc atc cag gaa ggg aca gtc   1234
Ala Ser Val Arg Pro Lys Val Leu Ser Ser Ile Gln Glu Gly Thr Val
260                 265                 270                 275

cct gac aac aca agc tca gca agg ggg aag gaa gac gtg aac aag acc   1282
Pro Asp Asn Thr Ser Ser Ala Arg Gly Lys Glu Asp Val Asn Lys Thr
                280                 285                 290

ctc cca aac ctt cag gta gtc aac cac cag caa ggc ccc cac cac aga   1330
Leu Pro Asn Leu Gln Val Val Asn His Gln Gln Gly Pro His His Arg
            295                 300                 305

cac atc ctg aag ctg ctg ccg tcc atg gag gcc act ggg ggc gag aag   1378
His Ile Leu Lys Leu Leu Pro Ser Met Glu Ala Thr Gly Gly Glu Lys
        310                 315                 320
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tcc agc acg ccc atc aag ggc ccc aag agg gga cat cct aga cag aac   1426
Ser Ser Thr Pro Ile Lys Gly Pro Lys Arg Gly His Pro Arg Gln Asn
    325                 330                 335

cta cac aag cat ttt gac atc aat gag cat ttg ccc tgg atg att gtg   1474
Leu His Lys His Phe Asp Ile Asn Glu His Leu Pro Trp Met Ile Val
340                 345                 350                 355

ctt ttc ctg ctg ctg gtg ctt gtg gtg att gtg gtg tgc agt atc cgg   1522
Leu Phe Leu Leu Leu Val Leu Val Val Ile Val Val Cys Ser Ile Arg
                360                 365                 370

aaa agc tcg agg act ctg aaa aag ggg ccc cgg cag gat ccc agt gcc   1570
Lys Ser Ser Arg Thr Leu Lys Lys Gly Pro Arg Gln Asp Pro Ser Ala
            375                 380                 385

att gtg gaa aag gca ggg ctg aag aaa tcc atg act cca acc cag aac   1618
Ile Val Glu Lys Ala Gly Leu Lys Lys Ser Met Thr Pro Thr Gln Asn
        390                 395                 400

cgg gag aaa tgg atc tac tac tgc aat ggc cat ggt atc gat atc ctg   1666
Arg Glu Lys Trp Ile Tyr Tyr Cys Asn Gly His Gly Ile Asp Ile Leu
    405                 410                 415

aag ctt gta gca gcc caa gtg gga agc cag tgg aaa gat atc tat cag   1714
Lys Leu Val Ala Ala Gln Val Gly Ser Gln Trp Lys Asp Ile Tyr Gln
420                 425                 430                 435

ttt ctt tgc aat gcc agt gag agg gag gtt gct gct ttc tcc aat ggg   1762
Phe Leu Cys Asn Ala Ser Glu Arg Glu Val Ala Ala Phe Ser Asn Gly
                440                 445                 450

tac aca gcc gac cac gag cgg gcc tac gca gct ctg cag cac tgg acc   1810
Tyr Thr Ala Asp His Glu Arg Ala Tyr Ala Ala Leu Gln His Trp Thr
            455                 460                 465

atc cgg ggc ccc gag gcc agc ctc gcc cag cta att agc gcc ctg cgc   1858
Ile Arg Gly Pro Glu Ala Ser Leu Ala Gln Leu Ile Ser Ala Leu Arg
        470                 475                 480

cag cac cgg aga aac gat gtt gtg gag aag att cgt ggg ctg atg gaa   1906
Gln His Arg Arg Asn Asp Val Val Glu Lys Ile Arg Gly Leu Met Glu
    485                 490                 495

gac acc acc cag ctg gaa act gac aaa cta gct ctc ccg atg agc ccc   1954
Asp Thr Thr Gln Leu Glu Thr Asp Lys Leu Ala Leu Pro Met Ser Pro
500                 505                 510                 515

agc ccg ctt agc ccg agc ccc atc ccc agc ccc aac gcg aaa ctt gag   2002
Ser Pro Leu Ser Pro Ser Pro Ile Pro Ser Pro Asn Ala Lys Leu Glu
                520                 525                 530

aat tcc gct ctc ctg acg gtg gag cct tcc cca cag gac aag aac aag   2050
Asn Ser Ala Leu Leu Thr Val Glu Pro Ser Pro Gln Asp Lys Asn Lys
            535                 540                 545

ggc ttc ttc gtg gat gag tcg gag ccc ctt ctc cgc tgt gac tct aca   2098
Gly Phe Phe Val Asp Glu Ser Glu Pro Leu Leu Arg Cys Asp Ser Thr
        550                 555                 560
```

```
tcc agc ggc tcc tcc gcg ctg agc agg aac ggt tcc ttt att acc aaa   2146
Ser Ser Gly Ser Ser Ala Leu Ser Arg Asn Gly Ser Phe Ile Thr Lys
    565                 570                 575

gaa aag aag gac aca gtg ttg cgg cag gta cgc ctg gac ccc tgt gac   2194
Glu Lys Lys Asp Thr Val Leu Arg Gln Val Arg Leu Asp Pro Cys Asp
580                 585                 590                 595

ttg cag cct atc ttt gat gac atg ctc cac ttt cta aat cct gag gag   2242
Leu Gln Pro Ile Phe Asp Asp Met Leu His Phe Leu Asn Pro Glu Glu
                600                 605                 610

ctg cgg gtg att gaa gag att ccc cag gct gag gac aaa cta gac cgg   2290
Leu Arg Val Ile Glu Glu Ile Pro Gln Ala Glu Asp Lys Leu Asp Arg
            615                 620                 625

cta ttc gaa att att gga gtc aag agc cag gaa gcc agc cag acc ctc   2338
Leu Phe Glu Ile Ile Gly Val Lys Ser Gln Glu Ala Ser Gln Thr Leu
        630                 635                 640

ctg gac tct gtt tat agc cat ctt cct gac ctg ctg tagaacatag        2384
Leu Asp Ser Val Tyr Ser His Leu Pro Asp Leu Leu
    645                 650                 655

ggatactgca ttctggaaat tactcaattt agtggcaggg tggtttttta atttccttct 2444

gtgtctgatt tttgttgttt ggggtgtgtg tgtgtgtttg tgtgtgtgtg tgtgtgtgtg 2504

tgtgtgtgtg tttaacagag aatatggcca gtgcttgagt tctttctcct tctctctctc 2564

tctttttttt ttaaataact cttctgggaa gttggtttat aagcctttgc caggtgtaac 2624

tgttgtgaaa tacccaccac taaagttttt taagttccat attttctcca ttttgccttc 2684

ttatgtattt tcaagattat tctgtgcact ttaaatttac tcaacttacc ataaatgcag 2744

tgtgactttt cccacacact ggattgtgag gctcttaact tcttaaaagt ataatggcat 2804

cttgtgaatc ctataagcag tctttatgtc tcttaacatt cacacctact ttttaaaaac 2864

aaatattatt act                                                    2877
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<210> 10
<211> 655
<212> PRT
<213> Unknown

<400> 10

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Met Gly Thr Ser Pro Ser Ser Ser Thr Ala Leu Ala Ser Cys Ser Arg
  1               5                  10                  15

Ile Ala Arg Arg Ala Thr Ala Thr Met Ile Ala Gly Ser Leu Leu Leu
            20                  25                  30

Leu Gly Phe Leu Ser Thr Thr Thr Ala Gln Pro Glu Gln Lys Ala Ser
        35                  40                  45

Asn Leu Ile Gly Thr Tyr Arg His Val Asp Arg Ala Thr Gly Gln Val
    50                  55                  60
```

```
Leu Thr Cys Asp Lys Cys Pro Ala Gly Thr Tyr Val Ser Glu His Cys
 65                  70                  75                  80

Thr Asn Thr Ser Leu Arg Val Cys Ser Ser Cys Pro Val Gly Thr Phe
                85                  90                  95

Thr Arg His Glu Asn Gly Ile Glu Lys Cys His Asp Cys Ser Gln Pro
            100                 105                 110

Cys Pro Trp Pro Met Ile Glu Lys Leu Pro Cys Ala Ala Leu Thr Asp
        115                 120                 125

Arg Glu Cys Thr Cys Pro Pro Gly Met Phe Gln Ser Asn Ala Thr Cys
    130                 135                 140

Ala Pro His Thr Val Cys Pro Val Gly Trp Gly Val Arg Lys Lys Gly
145                 150                 155                 160

Thr Glu Thr Glu Asp Val Arg Cys Lys Gln Cys Ala Arg Gly Thr Phe
                165                 170                 175

Ser Asp Val Pro Ser Ser Val Met Lys Cys Lys Ala Tyr Thr Asp Cys
            180                 185                 190

Leu Ser Gln Asn Leu Val Val Ile Lys Pro Gly Thr Lys Glu Thr Asp
        195                 200                 205

Asn Val Cys Gly Thr Leu Pro Ser Phe Ser Ser Ser Thr Ser Pro Ser
    210                 215                 220

Pro Gly Thr Ala Ile Phe Pro Arg Pro Glu His Met Glu Thr His Glu
225                 230                 235                 240

Val Pro Ser Ser Thr Tyr Val Pro Lys Gly Met Asn Ser Thr Glu Ser
                245                 250                 255

Asn Ser Ser Ala Ser Val Arg Pro Lys Val Leu Ser Ser Ile Gln Glu
            260                 265                 270

Gly Thr Val Pro Asp Asn Thr Ser Ser Ala Arg Gly Lys Glu Asp Val
        275                 280                 285

Asn Lys Thr Leu Pro Asn Leu Gln Val Val Asn His Gln Gln Gly Pro
    290                 295                 300

His His Arg His Ile Leu Lys Leu Leu Pro Ser Met Glu Ala Thr Gly
305                 310                 315                 320

Gly Glu Lys Ser Ser Thr Pro Ile Lys Gly Pro Lys Arg Gly His Pro
                325                 330                 335

Arg Gln Asn Leu His Lys His Phe Asp Ile Asn Glu His Leu Pro Trp
            340                 345                 350

Met Ile Val Leu Phe Leu Leu Leu Val Leu Val Val Ile Val Val Cys
        355                 360                 365

Ser Ile Arg Lys Ser Ser Arg Thr Leu Lys Lys Gly Pro Arg Gln Asp
    370                 375                 380
```

```
Pro Ser Ala Ile Val Glu Lys Ala Gly Leu Lys Lys Ser Met Thr Pro
385                 390                 395                 400

Thr Gln Asn Arg Glu Lys Trp Ile Tyr Tyr Cys Asn Gly His Gly Ile
                405                 410                 415

Asp Ile Leu Lys Leu Val Ala Ala Gln Val Gly Ser Gln Trp Lys Asp
            420                 425                 430

Ile Tyr Gln Phe Leu Cys Asn Ala Ser Glu Arg Glu Val Ala Ala Phe
        435                 440                 445

Ser Asn Gly Tyr Thr Ala Asp His Glu Arg Ala Tyr Ala Ala Leu Gln
    450                 455                 460

His Trp Thr Ile Arg Gly Pro Glu Ala Ser Leu Ala Gln Leu Ile Ser
465                 470                 475                 480

Ala Leu Arg Gln His Arg Arg Asn Asp Val Val Glu Lys Ile Arg Gly
                485                 490                 495

Leu Met Glu Asp Thr Thr Gln Leu Glu Thr Asp Lys Leu Ala Leu Pro
            500                 505                 510

Met Ser Pro Ser Pro Leu Ser Pro Ser Pro Ile Pro Ser Pro Asn Ala
        515                 520                 525

Lys Leu Glu Asn Ser Ala Leu Leu Thr Val Glu Pro Ser Pro Gln Asp
    530                 535                 540

Lys Asn Lys Gly Phe Phe Val Asp Glu Ser Glu Pro Leu Leu Arg Cys
545                 550                 555                 560

Asp Ser Thr Ser Ser Gly Ser Ser Ala Leu Ser Arg Asn Gly Ser Phe
                565                 570                 575

Ile Thr Lys Glu Lys Lys Asp Thr Val Leu Arg Gln Val Arg Leu Asp
            580                 585                 590

Pro Cys Asp Leu Gln Pro Ile Phe Asp Asp Met Leu His Phe Leu Asn
        595                 600                 605

Pro Glu Glu Leu Arg Val Ile Glu Glu Ile Pro Gln Ala Glu Asp Lys
    610                 615                 620

Leu Asp Arg Leu Phe Glu Ile Ile Gly Val Lys Ser Gln Glu Ala Ser
625                 630                 635                 640

Gln Thr Leu Leu Asp Ser Val Tyr Ser His Leu Pro Asp Leu Leu
                645                 650                 655
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<210> 11
<211> 1474
<212> DNA
<213> Unknown

<220>
<223> Description of Unknown Organism:primate

<220>

<221> CDS
<222> (1)..(1332)

<400> 11

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atg ggg acc tct ccg agc agc agc acc gcc ctc gcc tcc tgc agc cgc   48
Met Gly Thr Ser Pro Ser Ser Ser Thr Ala Leu Ala Ser Cys Ser Arg
  1               5                  10                  15

atc gcc cgc cga gcc aca gcc acg atg atc gcg ggc tcc ctt ctc ctg   96
Ile Ala Arg Arg Ala Thr Ala Thr Met Ile Ala Gly Ser Leu Leu Leu
             20                  25                  30

ctt gga ttc ctt agc acc acc aca gct cag cca gaa cag aag gcc tcg  144
Leu Gly Phe Leu Ser Thr Thr Thr Ala Gln Pro Glu Gln Lys Ala Ser
         35                  40                  45

aat ctc att ggc aca tac cgc cat gtt gac cgt gcc acc ggc cag gtg  192
Asn Leu Ile Gly Thr Tyr Arg His Val Asp Arg Ala Thr Gly Gln Val
     50                  55                  60

cta acc tgt gac aag tgt cca gca gga acc tat gtc tct gag cat tgt  240
Leu Thr Cys Asp Lys Cys Pro Ala Gly Thr Tyr Val Ser Glu His Cys
 65                  70                  75                  80

acc aac aca agc ctg cgc gtc tgc agc agt tgc cct gtg ggg acc ttt  288
Thr Asn Thr Ser Leu Arg Val Cys Ser Ser Cys Pro Val Gly Thr Phe
                 85                  90                  95

acc agg cat gag aat ggc ata gag aaa tgc cat gac tgt agt cag cca  336
Thr Arg His Glu Asn Gly Ile Glu Lys Cys His Asp Cys Ser Gln Pro
            100                 105                 110

tgc cca tgg cca atg att gag aaa tta cct tgt gct gcc ttg act gac  384
Cys Pro Trp Pro Met Ile Glu Lys Leu Pro Cys Ala Ala Leu Thr Asp
        115                 120                 125

cga gaa tgc act tgc cca cct ggc atg ttc cag tct aac gct acc tgt  432
Arg Glu Cys Thr Cys Pro Pro Gly Met Phe Gln Ser Asn Ala Thr Cys
    130                 135                 140

gcc ccc cat acg gtg tgt cct gtg ggt tgg ggt gtg cgg aag aaa ggg  480
Ala Pro His Thr Val Cys Pro Val Gly Trp Gly Val Arg Lys Lys Gly
145                 150                 155                 160

aca gag act gag gat gtg cgg tgt aag cag tgt gct cgg ggt acc ttc  528
Thr Glu Thr Glu Asp Val Arg Cys Lys Gln Cys Ala Arg Gly Thr Phe
                165                 170                 175

tca gat gtg cct tct agt gtg atg aaa tgc aaa gca tac aca gac tgt  576
Ser Asp Val Pro Ser Ser Val Met Lys Cys Lys Ala Tyr Thr Asp Cys
            180                 185                 190

ctg agt cag aac ctg gtg gtg atc aag ccg ggg acc aag gag aca gac  624
Leu Ser Gln Asn Leu Val Val Ile Lys Pro Gly Thr Lys Glu Thr Asp
        195                 200                 205

aac gtc tgt ggc aca ctc ccg tcc ttc tcc agc tcc acc tca cct tcc  672
Asn Val Cys Gly Thr Leu Pro Ser Phe Ser Ser Ser Thr Ser Pro Ser
    210                 215                 220
```

```
cct ggc aca gcc atc ttt cca cgc cct gag cac atg gaa acc cat gaa   720
Pro Gly Thr Ala Ile Phe Pro Arg Pro Glu His Met Glu Thr His Glu
225                 230                 235                 240

gtc cct tcc tcc act tat gtt ccc aaa ggc atg aac tca aca gaa tcc   768
Val Pro Ser Ser Thr Tyr Val Pro Lys Gly Met Asn Ser Thr Glu Ser
                245                 250                 255

aac tct tct gcc tct gtt aga cca aag gta ctg agt agc atc cag gaa   816
Asn Ser Ser Ala Ser Val Arg Pro Lys Val Leu Ser Ser Ile Gln Glu
            260                 265                 270

ggg aca gtc cct gac aac aca agc tca gca agg ggg aag gaa gac gtg   864
Gly Thr Val Pro Asp Asn Thr Ser Ser Ala Arg Gly Lys Glu Asp Val
        275                 280                 285

aac aag acc ctc cca aac ctt cag gta gtc aac cac cag caa ggc ccc   912
Asn Lys Thr Leu Pro Asn Leu Gln Val Val Asn His Gln Gln Gly Pro
    290                 295                 300

cac cac aga cac atc ctg aag ctg ctg ccg tcc atg gag gcc act ggg   960
His His Arg His Ile Leu Lys Leu Leu Pro Ser Met Glu Ala Thr Gly
305                 310                 315                 320

ggc gag aag tcc agc acg ccc atc aag ggc ccc aag agg gga cat cct  1008
Gly Glu Lys Ser Ser Thr Pro Ile Lys Gly Pro Lys Arg Gly His Pro
                325                 330                 335

aga cag aac cta cac aag cat ttt gac atc aat gag cat ttg ccc tgg  1056
Arg Gln Asn Leu His Lys His Phe Asp Ile Asn Glu His Leu Pro Trp
            340                 345                 350

atg att gtg ctt ttc ctg ctg ctg gtg ctt gtg gtg att gtg gtg tgc  1104
Met Ile Val Leu Phe Leu Leu Leu Val Leu Val Val Ile Val Val Cys
        355                 360                 365

agt atc cgg aaa agc tcg agg act ctg aaa aag ggg ccc cgg cag gat  1152
Ser Ile Arg Lys Ser Ser Arg Thr Leu Lys Lys Gly Pro Arg Gln Asp
    370                 375                 380

ccc agt gcc att gtg gaa aag gca ggg ctg aag aaa tcc atg act cca  1200
Pro Ser Ala Ile Val Glu Lys Ala Gly Leu Lys Lys Ser Met Thr Pro
385                 390                 395                 400

acc cag aac cgg gag aaa tgg atc tac tac tgc aat ggc cat gga ccc  1248
Thr Gln Asn Arg Glu Lys Trp Ile Tyr Tyr Cys Asn Gly His Gly Pro
                405                 410                 415

cat gat gag gag tgg ggg ttg atg gag aga cat att caa gat att tat  1296
His Asp Glu Glu Trp Gly Leu Met Glu Arg His Ile Gln Asp Ile Tyr
            420                 425                 430

att caa aga agc aat caa gat tca gaa aga tgg ggt tgataatttt       1342
Ile Gln Arg Ser Asn Gln Asp Ser Glu Arg Trp Gly
        435                 440

tacttcaccc tgggaggcag catagtgcag tgaaaggtat cgatatcctg aagcttgtag 1402

cagcccaagt gggaagccag tggaaagata tctatcagtt tctttgcaat gccagtgaga 1462

gggaggttgc tg                                                    1474
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<210> 12
<211> 444
<212> PRT
<213> Unknown

<400> 12

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Met Gly Thr Ser Pro Ser Ser Ser Thr Ala Leu Ala Ser Cys Ser Arg
 1               5                  10                  15

Ile Ala Arg Arg Ala Thr Ala Thr Met Ile Ala Gly Ser Leu Leu Leu
            20                  25                  30

Leu Gly Phe Leu Ser Thr Thr Thr Ala Gln Pro Glu Gln Lys Ala Ser
        35                  40                  45

Asn Leu Ile Gly Thr Tyr Arg His Val Asp Arg Ala Thr Gly Gln Val
    50                  55                  60

Leu Thr Cys Asp Lys Cys Pro Ala Gly Thr Tyr Val Ser Glu His Cys
65                  70                  75                  80

Thr Asn Thr Ser Leu Arg Val Cys Ser Ser Cys Pro Val Gly Thr Phe
                85                  90                  95

Thr Arg His Glu Asn Gly Ile Glu Lys Cys His Asp Cys Ser Gln Pro
            100                 105                 110

Cys Pro Trp Pro Met Ile Glu Lys Leu Pro Cys Ala Ala Leu Thr Asp
        115                 120                 125

Arg Glu Cys Thr Cys Pro Pro Gly Met Phe Gln Ser Asn Ala Thr Cys
    130                 135                 140

Ala Pro His Thr Val Cys Pro Val Gly Trp Gly Val Arg Lys Lys Gly
145                 150                 155                 160

Thr Glu Thr Glu Asp Val Arg Cys Lys Gln Cys Ala Arg Gly Thr Phe
                165                 170                 175

Ser Asp Val Pro Ser Ser Val Met Lys Cys Lys Ala Tyr Thr Asp Cys
            180                 185                 190

Leu Ser Gln Asn Leu Val Val Ile Lys Pro Gly Thr Lys Glu Thr Asp
        195                 200                 205

Asn Val Cys Gly Thr Leu Pro Ser Phe Ser Ser Ser Thr Ser Pro Ser
    210                 215                 220

Pro Gly Thr Ala Ile Phe Pro Arg Pro Glu His Met Glu Thr His Glu
225                 230                 235                 240

Val Pro Ser Ser Thr Tyr Val Pro Lys Gly Met Asn Ser Thr Glu Ser
                245                 250                 255

Asn Ser Ser Ala Ser Val Arg Pro Lys Val Leu Ser Ser Ile Gln Glu
            260                 265                 270

Gly Thr Val Pro Asp Asn Thr Ser Ser Ala Arg Gly Lys Glu Asp Val
        275                 280                 285
```

Asn Lys Thr Leu Pro Asn Leu Gln Val Val Asn His Gln Gln Gly Pro
290 295 300

His His Arg His Ile Leu Lys Leu Leu Pro Ser Met Glu Ala Thr Gly
305 310 315 320

Gly Glu Lys Ser Ser Thr Pro Ile Lys Gly Pro Lys Arg Gly His Pro
325 330 335

Arg Gln Asn Leu His Lys His Phe Asp Ile Asn Glu His Leu Pro Trp
340 345 350

Met Ile Val Leu Phe Leu Leu Leu Val Leu Val Val Ile Val Val Cys
355 360 365

Ser Ile Arg Lys Ser Ser Arg Thr Leu Lys Lys Gly Pro Arg Gln Asp
370 375 380

Pro Ser Ala Ile Val Glu Lys Ala Gly Leu Lys Lys Ser Met Thr Pro
385 390 395 400

Thr Gln Asn Arg Glu Lys Trp Ile Tyr Tyr Cys Asn Gly His Gly Pro
405 410 415

His Asp Glu Glu Trp Gly Leu Met Glu Arg His Ile Gln Asp Ile Tyr
420 425 430

Ile Gln Arg Ser Asn Gln Asp Ser Glu Arg Trp Gly
435 440

<210> 13
<211> 227
<212> PRT
<213> Unknown

<220>
<223> Description of Unknown Organism:rodent

<400> 13
Met Ala Pro Ala Ala Leu Trp Val Ala Leu Val Phe Glu Leu Gln Leu
1 5 10 15

Trp Ala Thr Gly His Thr Val Pro Ala Gln Val Val Leu Thr Pro Tyr
20 25 30

Lys Pro Glu Pro Gly Tyr Glu Cys Gln Ile Ser Gln Glu Tyr Tyr Asp
35 40 45

Arg Lys Ala Gln Met Cys Cys Ala Lys Cys Pro Pro Gly Gln Tyr Val
50 55 60

Lys His Phe Cys Asn Lys Thr Ser Asp Thr Val Cys Ala Asp Cys Glu
65 70 75 80

Ala Ser Met Tyr Thr Gln Val Trp Asn Gln Phe Arg Thr Cys Leu Ser
85 90 95

Cys Ser Ser Ser Cys Thr Thr Asp Gln Val Glu Ile Arg Ala Cys Thr
100 105 110

Lys Gln Gln Asn Arg Val Cys Ala Cys Glu Ala Gly Arg Tyr Cys Ala
115 120 125

Leu Lys Thr His Ser Gly Ser Cys Arg Gln Cys Met Arg Leu Ser Lys
130 135 140

Cys Gly Pro Gly Phe Gly Val Ala Ser Ser Arg Ala Pro Asn Gly Asn
145 150 155 160

Val Leu Cys Lys Ala Cys Ala Pro Gly Thr Phe Ser Asp Thr Thr Ser
165 170 175

Ser Thr Asp Val Cys Arg Pro His Arg Ile Cys Ser Ile Leu Ala Ile
180 185 190

Pro Gly Asn Ala Ser Thr Asp Ala Val Cys Ala Pro Glu Ser Pro Thr
195 200 205

Leu Ser Ala Ile Pro Arg Thr Leu Tyr Val Ser Gln Pro Glu Pro Thr
210 215 220

Arg Ser Gln
225

<210> 14
<211> 225
<212> PRT
<213> Unknown

<220>
<223> Description of Unknown Organism:primate

<400> 14
Met Ala Pro Val Ala Val Trp Ala Ala Leu Ala Val Gly Leu Glu Leu
1 5 10 15

Trp Ala Ala Ala His Ala Leu Pro Ala Gln Val Ala Phe Thr Pro Tyr
20 25 30

Ala Pro Glu Pro Gly Ser Thr Cys Arg Leu Arg Glu Tyr Tyr Asp Gln
35 40 45

Thr Ala Gln Met Cys Cys Ser Lys Cys Ser Pro Gly Gln His Ala Lys
50 55 60

Val Phe Cys Thr Lys Thr Ser Asp Thr Val Cys Asp Ser Cys Glu Asp
65 70 75 80

Ser Thr Tyr Thr Gln Leu Trp Asn Trp Val Pro Glu Cys Leu Ser Cys
85 90 95

Gly Ser Arg Cys Ser Ser Asp Gln Val Glu Thr Gln Ala Cys Thr Arg
100 105 110

Glu Gln Asn Arg Ile Cys Thr Cys Arg Pro Gly Trp Tyr Cys Ala Leu
115 120 125

Ser Lys Gln Glu Gly Cys Arg Leu Cys Ala Pro Leu Arg Lys Cys Arg
130 135 140

Pro Gly Phe Gly Val Ala Arg Pro Gly Thr Glu Thr Ser Asp Val Val
145 150 155 160

Cys Lys Pro Cys Ala Pro Gly Thr Phe Ser Asn Thr Thr Ser Ser Thr
165 170 175

Asp Ile Cys Arg Pro His Gln Ile Cys Asn Val Val Ala Ile Pro Gly
180 185 190

Asn Ala Ser Met Asp Ala Val Cys Thr Ser Thr Ser Pro Thr Arg Ser
195 200 205

Met Ala Pro Gly Ala Val His Leu Pro Gln Pro Val Ser Thr Arg Ser
210 215 220

Gln
225

<210> 15
<211> 187
<212> PRT
<213> Unknown

<220>
<223> Description of Unknown Organism:primate

<400> 15
Met Asn Lys Leu Leu Cys Cys Ala Leu Val Phe Leu Asp Ile Ser Ile
1 5 10 15

Lys Trp Thr Thr Gln Glu Thr Phe Pro Pro Lys Tyr Leu His Tyr Asp
20 25 30

Glu Glu Thr Ser His Gln Leu Leu Cys Asp Lys Cys Pro Pro Gly Thr
35 40 45

Tyr Leu Lys Gln His Cys Thr Ala Lys Trp Lys Thr Val Cys Ala Pro
50 55 60

Cys Pro Asp His Tyr Tyr Thr Asp Ser Trp His Thr Ser Asp Glu Cys
65 70 75 80

Leu Tyr Cys Ser Pro Val Cys Lys Glu Leu Gln Tyr Val Lys Gln Glu
85 90 95

Cys Asn Arg Thr His Asn Arg Val Cys Glu Cys Lys Glu Gly Arg Tyr
100 105 110

Leu Glu Ile Glu Phe Cys Leu Lys His Arg Ser Cys Pro Pro Gly Phe
115 120 125

Gly Val Val Gln Ala Gly Thr Pro Glu Arg Asn Thr Val Cys Lys Arg
130 135 140

Cys Pro Asp Gly Phe Phe Ser Asn Glu Thr Ser Ser Lys Ala Pro Cys
145 150 155 160

Arg Lys His Thr Asn Cys Ser Val Phe Gly Leu Leu Leu Thr Gln Lys
165 170 175

Gly Asn Ala Thr His Asp Asn Ile Cys Ser Gly
180 185

<210> 16
<211> 636
<212> DNA
<213> Unknown

<220>
<223> Description of Unknown Organism:rodent

<220>
<221> CDS
<222> (104)..(553)

<400> 16
ggcacgaggg cgtttggcgc ggaagtgcta ccaagctgcg gaaagcgtga gtctggagca 60

cagcactggc gagtagcagg aataaacacg tttggtgaga gcc atg gca ctc aag 115
Met Ala Leu Lys
1

gtc cta cct cta cac agg acg gtg ctc ttc gct gcc att ctc ttc cta 163
Val Leu Pro Leu His Arg Thr Val Leu Phe Ala Ala Ile Leu Phe Leu
5 10 15 20

ctc cac ctg gca tgt aaa gtg agt tgc gaa acc gga gat tgc agg cag 211
Leu His Leu Ala Cys Lys Val Ser Cys Glu Thr Gly Asp Cys Arg Gln
25 30 35

cag gaa ttc aag gat cga tct gga aac tgt gtc ctc tgc aaa cag tgc 259
Gln Glu Phe Lys Asp Arg Ser Gly Asn Cys Val Leu Cys Lys Gln Cys
40 45 50

gga cct ggc atg gag ttg tcc aag gaa tgt ggc ttc ggc tat ggg gag 307
Gly Pro Gly Met Glu Leu Ser Lys Glu Cys Gly Phe Gly Tyr Gly Glu
55 60 65

gat gca cag tgt gtg ccc tgc agg ccg cac cgg ttc aag gaa gac tgg 355
Asp Ala Gln Cys Val Pro Cys Arg Pro His Arg Phe Lys Glu Asp Trp
70 75 80

ggt ttc cag aag tgt aag cca tgt gcg gac tgt gcg ctg gtg aac cgc 403
Gly Phe Gln Lys Cys Lys Pro Cys Ala Asp Cys Ala Leu Val Asn Arg
85 90 95 100

ttt cag agg gcc aac tgc tca cac acc agt gat gct gtc tgc ggg gac 451
Phe Gln Arg Ala Asn Cys Ser His Thr Ser Asp Ala Val Cys Gly Asp
105 110 115

tgc ctg cca gga ttt tac cgg aag acc aaa ctg gtt ggt ttt caa gac 499
Cys Leu Pro Gly Phe Tyr Arg Lys Thr Lys Leu Val Gly Phe Gln Asp
120 125 130

atg gag tgt gtg ccc tgc gga gac cca cct cct ccc tac gaa cca cac 547
Met Glu Cys Val Pro Cys Gly Asp Pro Pro Pro Pro Tyr Glu Pro His
135 140 145

tgt gag tgatgtgcca agtggcagca gacctttaaa aaaaaaagaa aaaaaaacaa 603
Cys Glu
150

acaaaaacaa aaaaaaaaaa aaaaaaaaaa aaa 636

<210> 17
<211> 150
<212> PRT
<213> Unknown

<400> 17
Met Ala Leu Lys Val Leu Pro Leu His Arg Thr Val Leu Phe Ala Ala
1 5 10 15

Ile Leu Phe Leu Leu His Leu Ala Cys Lys Val Ser Cys Glu Thr Gly
20 25 30

Asp Cys Arg Gln Gln Glu Phe Lys Asp Arg Ser Gly Asn Cys Val Leu
35 40 45

Cys Lys Gln Cys Gly Pro Gly Met Glu Leu Ser Lys Glu Cys Gly Phe
50 55 60

Gly Tyr Gly Glu Asp Ala Gln Cys Val Pro Cys Arg Pro His Arg Phe
65 70 75 80

Lys Glu Asp Trp Gly Phe Gln Lys Cys Lys Pro Cys Ala Asp Cys Ala
85 90 95

Leu Val Asn Arg Phe Gln Arg Ala Asn Cys Ser His Thr Ser Asp Ala
100 105 110

Val Cys Gly Asp Cys Leu Pro Gly Phe Tyr Arg Lys Thr Lys Leu Val
115 120 125

Gly Phe Gln Asp Met Glu Cys Val Pro Cys Gly Asp Pro Pro Pro Pro
130 135 140

Tyr Glu Pro His Cys Glu
145 150

<210> 18
<211> 474
<212> DNA
<213> Unknown

<220>
<223> Description of Unknown Organism:primate

<220>
<221> CDS
<222> (78)..(473)

<400> 18

cgcgctgagg tggatttgta ccggagtccc atttgggagc aagagccatc tactcgtccg 60
ttaccggcct tcccacc atg gat tgc caa gaa aat gag tac tgg gac caa 110

```
                    Met Asp Cys Gln Glu Asn Glu Tyr Trp Asp Gln
                      1               5                  10

tgg gga cgg tgt gtc acc tgc caa cgg tgt ggt cct gga cag gag cta   158
Trp Gly Arg Cys Val Thr Cys Gln Arg Cys Gly Pro Gly Gln Glu Leu
               15                  20                  25

tcc aag gat tgt ggt tat gga gag ggt gga gat gcc tac tgc aca gcc   206
Ser Lys Asp Cys Gly Tyr Gly Glu Gly Gly Asp Ala Tyr Cys Thr Ala
          30                  35                  40

tgc cct cct cgc agt aca aaa gca gct ggg gcc acc aca aat gtc aga   254
Cys Pro Pro Arg Ser Thr Lys Ala Ala Gly Ala Thr Thr Asn Val Arg
      45                  50                  55

gtt gca tca cct gtg ctg tca tca atc gtg ttc aga agg ttc aac tgc   302
Val Ala Ser Pro Val Leu Ser Ser Ile Val Phe Arg Arg Phe Asn Cys
  60                  65                  70                  75

aca gtn acc tct nat gct gtc tgt ggg gga ngg ttt gcc caa gtt tct   350
Thr Xaa Thr Ser Xaa Ala Val Cys Gly Gly Xaa Phe Ala Gln Val Ser
                  80                  85                  90

aac cga aag aca cgc cat tgg aag gct gcc agg acc aag gat ggc atc   398
Asn Arg Lys Thr Arg His Trp Lys Ala Ala Arg Thr Lys Asp Gly Ile
              95                  100                 105

ccg tgg cac aaa gnc aga ccc cca act tct gan ggt tnc aaa gtg nct   446
Pro Trp His Lys Xaa Arg Pro Pro Thr Ser Xaa Gly Xaa Lys Val Xaa
          110                 115                 120

ttc caa ttg gag ctt aat ggg agg can a                            474
Phe Gln Leu Glu Leu Asn Gly Arg Xaa
      125                 130
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<210> 19
<211> 132
<212> PRT
<213> Unknown

<400> 19

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Met Asp Cys Gln Glu Asn Glu Tyr Trp Asp Gln Trp Gly Arg Cys Val
  1               5                  10                  15

Thr Cys Gln Arg Cys Gly Pro Gly Gln Glu Leu Ser Lys Asp Cys Gly
              20                  25                  30

Tyr Gly Glu Gly Gly Asp Ala Tyr Cys Thr Ala Cys Pro Pro Arg Ser
          35                  40                  45

Thr Lys Ala Ala Gly Ala Thr Thr Asn Val Arg Val Ala Ser Pro Val
      50                  55                  60

Leu Ser Ser Ile Val Phe Arg Arg Phe Asn Cys Thr Xaa Thr Ser Xaa
  65                  70                  75                  80

Ala Val Cys Gly Gly Xaa Phe Ala Gln Val Ser Asn Arg Lys Thr Arg
                  85                  90                  95
```

His Trp Lys Ala Ala Arg Thr Lys Asp Gly Ile Pro Trp His Lys Xaa
100 105 110

Arg Pro Pro Thr Ser Xaa Gly Xaa Lys Val Xaa Phe Gln Leu Glu Leu
115 120 125

Asn Gly Arg Xaa
130

<210> 20
<211> 546
<212> DNA
<213> Unknown

<220>
<223> Description of Unknown Organism:primate

<220>
<221> CDS
<222> (78)..(308)

<400> 20
cgcgctgagg tggatttgta ccggagtccc atttgggagc aagagccatc tactcgtccg 60

ttaccggcct tcccacc atg gat tgc caa gaa aat gag tac tgg gac caa 110
Met Asp Cys Gln Glu Asn Glu Tyr Trp Asp Gln
1 5 10

tgg gga cgg tgt gtc acc tgc caa cgg tgt ggt cct gga cag gag cta 158
Trp Gly Arg Cys Val Thr Cys Gln Arg Cys Gly Pro Gly Gln Glu Leu
15 20 25

tcc aag gat tgt ggt tat gga gag ggt gga gat gcc tac tgc aca gcc 206
Ser Lys Asp Cys Gly Tyr Gly Glu Gly Gly Asp Ala Tyr Cys Thr Ala
30 35 40

tgc cct cct cgc agg tac aaa agc agc tgg ggc cac cac aaa tgt cag 254
Cys Pro Pro Arg Arg Tyr Lys Ser Ser Trp Gly His His Lys Cys Gln
45 50 55

agt tgc atc acc tgt gct gtc atc aat cgt gtt cag aag gtc caa ctg 302
Ser Cys Ile Thr Cys Ala Val Ile Asn Arg Val Gln Lys Val Gln Leu
60 65 70 75

cac agc taacctctna tgctgtctgt ggggatgttt gncccaagtt ctnaccgaaa 358
His Ser

agacacgcca tgggaaggct ggcaggacca ngaatggccn tcccgtggca gaaagccaga 418

ccccccaacn nctgnaggtt ccaatgtggc cttnccattt ggaagcttan tgggaaggca 478

gatgncaacc caaagtggcc ccttcaggga ggccaaaatt tgttggcaat gggtgnagca 538

gcntgcca 546

<210> 21
<211> 77
<212> PRT
<213> Unknown
<400> 21

Met Asp Cys Gln Glu Asn Glu Tyr Trp Asp Gln Trp Gly Arg Cys Val
1 5 10 15

Thr Cys Gln Arg Cys Gly Pro Gly Gln Glu Leu Ser Lys Asp Cys Gly
20 25 30

Tyr Gly Glu Gly Gly Asp Ala Tyr Cys Thr Ala Cys Pro Pro Arg Arg
35 40 45

Tyr Lys Ser Ser Trp Gly His His Lys Cys Gln Ser Cys Ile Thr Cys
50 55 60

Ala Val Ile Asn Arg Val Gln Lys Val Gln Leu His Ser
65 70 75

<210> 22
<211> 932
<212> DNA
<213> Unknown

<220>
<223> Description of Unknown Organism:primate

<220>
<221> CDS
<222> (78)..(770)

<220>
<221> misc_feature
<222> (782)
<223> nucleotide may be A, C, G, or T

<400> 22
cgcgctgagg tggatttgta ccggagtccc atttgggagc aagagccatc tactcgtccg 60

ttaccggcct tcccacc atg gat tgc caa gaa aat gag tac tgg gac caa 110
Met Asp Cys Gln Glu Asn Glu Tyr Trp Asp Gln
1 5 10

tgg gga cgg tgt gtc acc tgc caa cgg tgt ggt cct gga cag gag cta 158
Trp Gly Arg Cys Val Thr Cys Gln Arg Cys Gly Pro Gly Gln Glu Leu
15 20 25

tcc aag gat tgt ggt tat gga gag ggt gga gat gcc tac tgc aca gcc 206
Ser Lys Asp Cys Gly Tyr Gly Glu Gly Gly Asp Ala Tyr Cys Thr Ala
30 35 40

tgc cct cct cgc agg tac aaa agc agc tgg ggc cac cac aaa tgt cag 254
Cys Pro Pro Arg Arg Tyr Lys Ser Ser Trp Gly His His Lys Cys Gln
45 50 55

```
agt tgc atc acc tgt gct gtc atc aat cgt gtt cag aag gtc aac tgc   302
Ser Cys Ile Thr Cys Ala Val Ile Asn Arg Val Gln Lys Val Asn Cys
 60                  65                  70                  75

aca gct acc tct aat gct gtc tgt ggg gac tgt ttg ccc agg ttc tac   350
Thr Ala Thr Ser Asn Ala Val Cys Gly Asp Cys Leu Pro Arg Phe Tyr
                 80                  85                  90

cga aag aca cgc att gga ggc ctg cag gac caa gag tgc atc ccg tgc   398
Arg Lys Thr Arg Ile Gly Gly Leu Gln Asp Gln Glu Cys Ile Pro Cys
             95                 100                 105

acg aag cag acc ccc acc tct gag gtt caa tgt gcc ttc cag ttg agc   446
Thr Lys Gln Thr Pro Thr Ser Glu Val Gln Cys Ala Phe Gln Leu Ser
        110                 115                 120

tta gtg gag gca gat gca ccc aca gtg ccc cct cag gag gcc aca ctt   494
Leu Val Glu Ala Asp Ala Pro Thr Val Pro Pro Gln Glu Ala Thr Leu
    125                 130                 135

gtt gca ctg gtg agc agc ctg cta gtg gtg ttt acc ctg gcc ttc ctg   542
Val Ala Leu Val Ser Ser Leu Leu Val Val Phe Thr Leu Ala Phe Leu
140                 145                 150                 155

ggg ctc ttc ttc ctc tac tgc aag cag ttc ttc aac aga cat tgc cag   590
Gly Leu Phe Phe Leu Tyr Cys Lys Gln Phe Phe Asn Arg His Cys Gln
                160                 165                 170

cgt gga ggt ttg ctg cag ttt gag gct gat aaa aca gca aag gag gaa   638
Arg Gly Gly Leu Leu Gln Phe Glu Ala Asp Lys Thr Ala Lys Glu Glu
            175                 180                 185

tct ctc ttc ccc gtg cca ccc agc aag gag acc agt gct gag tcc caa   686
Ser Leu Phe Pro Val Pro Pro Ser Lys Glu Thr Ser Ala Glu Ser Gln
        190                 195                 200

gtc tct tgg gcc cct ggc agc ctt gcc cag ttg ttc tct ctg gac tct   734
Val Ser Trp Ala Pro Gly Ser Leu Ala Gln Leu Phe Ser Leu Asp Ser
    205                 210                 215

gtt cct ata cca caa cag cag cag ggg cct gaa atg tgatgtccac        780
Val Pro Ile Pro Gln Gln Gln Gln Gly Pro Glu Met
220                 225                 230

angagctaat accctacaga tggggcatat cctatcccat cccaccagag gattgattct 840

ccatttcaca aggactgatc tggagcattt cttgcttccc tgttgtagtc tggggagcca 900

gattccacat tcatgggact accagacatg tt                              932


<210> 23
<211> 231
<212> PRT
<213> Unknown

<400> 23


Met Asp Cys Gln Glu Asn Glu Tyr Trp Asp Gln Trp Gly Arg Cys Val
  1               5                  10                  15
```

Thr Cys Gln Arg Cys Gly Pro Gly Gln Glu Leu Ser Lys Asp Cys Gly
20 25 30

Tyr Gly Glu Gly Gly Asp Ala Tyr Cys Thr Ala Cys Pro Pro Arg Arg
35 40 45

Tyr Lys Ser Ser Trp Gly His His Lys Cys Gln Ser Cys Ile Thr Cys
50 55 60

Ala Val Ile Asn Arg Val Gln Lys Val Asn Cys Thr Ala Thr Ser Asn
65 70 75 80

Ala Val Cys Gly Asp Cys Leu Pro Arg Phe Tyr Arg Lys Thr Arg Ile
85 90 95

Gly Gly Leu Gln Asp Gln Glu Cys Ile Pro Cys Thr Lys Gln Thr Pro
100 105 110

Thr Ser Glu Val Gln Cys Ala Phe Gln Leu Ser Leu Val Glu Ala Asp
115 120 125

Ala Pro Thr Val Pro Pro Gln Glu Ala Thr Leu Val Ala Leu Val Ser
130 135 140

Ser Leu Leu Val Val Phe Thr Leu Ala Phe Leu Gly Leu Phe Phe Leu
145 150 155 160

Tyr Cys Lys Gln Phe Phe Asn Arg His Cys Gln Arg Gly Gly Leu Leu
165 170 175

Gln Phe Glu Ala Asp Lys Thr Ala Lys Glu Glu Ser Leu Phe Pro Val
180 185 190

Pro Pro Ser Lys Glu Thr Ser Ala Glu Ser Gln Val Ser Trp Ala Pro
195 200 205

Gly Ser Leu Ala Gln Leu Phe Ser Leu Asp Ser Val Pro Ile Pro Gln
210 215 220

Gln Gln Gln Gly Pro Glu Met
225 230

<210> 24
<211> 232
<212> DNA
<213> Unknown

<220>
<223> Description of Unknown Organism:primate

<400> 24
ttggccttag ggaccaagct tttatcatcg tcagtgggac ttaacctgtc ttaaaagtgc 60

tgcttctcct acactcgctc aagatcccga gtcagctgta ttatggcatc ctattagtca 120

ggcagcctgt gcttcaagcc cgtagttgta ttcatcccct aaaggggcca ttccgtttgt 180

atcatcacat gtcctcagtg ggtccatgtg tatatcaagg acatgatgca ga 232

<210> 25
<211> 77
<212> PRT
<213> Unknown

<220>

<223> Description of Unknown Organism:primate

<400> 25
Leu Ala Leu Gly Thr Lys Leu Leu Ser Ser Ser Val Gly Leu Asn Leu
1 5 10 15

Ser Xaa Lys Cys Cys Phe Ser Tyr Thr Arg Ser Arg Ser Arg Val Ser
20 25 30

Cys Ile Met Ala Ser Tyr Xaa Ser Gly Ser Leu Cys Phe Lys Pro Val
35 40 45

Val Val Phe Ile Pro Xaa Arg Gly His Ser Val Cys Ile Ile Thr Cys
50 55 60

Pro Gln Trp Val His Val Tyr Ile Lys Asp Met Met Gln
65 70 75

<210> 26
<211> 72
<212> PRT
<213> Unknown

<220>
<223> Description of Unknown Organism:primate

<400> 26
Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro Ser Glu Cys
1 5 10 15

Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg Ile Met Asp
20 25 30

Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile Val Phe Ile
35 40 45

Thr Xaa Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp Lys Trp Val
50 55 60

Gln Asp Tyr Ile Lys Asp Met Lys
65 70

<210> 27
<211> 143
<212> PRT
<213> Unknown

<220>
<223> Description of Unknown Organism:primate

<400> 27
Met Lys Ile Ser Val Ala Ala Ile Pro Phe Phe Leu Leu Ile Thr Ile
1 5 10 15

```
Ala Leu Gly Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro
                20                  25                  30

Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg
            35                  40                  45

Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile
        50                  55                  60

Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp
65                  70                  75                  80

Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn Thr Lys Thr
                85                  90                  95

Glu Ser Ser Ser Arg Gly Pro Tyr His Pro Ser Glu Cys Cys Phe Thr
            100                 105                 110

Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg Ile Met Asp Tyr Tyr Glu
        115                 120                 125

Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile Val Phe Ile Thr Xaa
    130                 135                 140
```

<210> 28
<211> 93
<212> PRT
<213> Unknown

<220>
<223> Description of Unknown Organism:primate

<400> 28

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Met Lys Ile Ser Val Ala Ala Ile Pro Phe Phe Leu Leu Ile Thr Ile
  1               5                  10                  15

Ala Leu Gly Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro
            20                  25                  30

Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg
        35                  40                  45

Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile
    50                  55                  60

Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp
65                  70                  75                  80

Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn
                85                  90
```

<210> 29
<211> 93
<212> PRT
<213> Unknown

<220>
<223> Description of Unknown Organism:primate
<400> 29

```
Met Lys Ile Ser Val Ala Ala Ile Pro Phe Phe Leu Leu Ile Thr Ile
 1               5                  10                  15

Ala Leu Gly Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro
            20                  25                  30

Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg
        35                  40                  45

Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile
    50                  55                  60

Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp
65                  70                  75                  80

Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn
                85                  90
```

<210> 30
<211> 93
<212> PRT
<213> Unknown

<220>
<223> Description of Unknown Organism:primate

<400> 30

```
Met Lys Ile Ser Val Ala Ala Ile Pro Phe Phe Leu Leu Ile Thr Ile
 1               5                  10                  15

Ala Leu Gly Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro
            20                  25                  30

Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg
        35                  40                  45

Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile
    50                  55                  60

Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp
65                  70                  75                  80

Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn
                85                  90
```

<210> 31
<211> 1082
<212> DNA
<213> Unknown

<220>
<223> Description of Unknown Organism:primate

<220>
<221> CDS
<222> (1)..(1080)

<220>
<221> misc_feature

<222> (20)
<223> nucleotide may be G

<220>
<221> misc_feature
<222> (56)
<223> nucleotide may be A, C, G or T

<220>
<221> misc_feature
<222> (103)
<223> nucleotide may be A, C, G, or T

<220>
<221> misc_feature
<222> (130)
<223> nucleotide may be C or T

<220>
<221> misc_feature
<222> (190)
<223> nucleotide may be A or C

<220>
<221> misc_feature
<222> (256)
<223> nucleotide may be C or G

<400> 31

```
atg cct ttc ccc ggc cca cac gca ggt aga tct tcc act cta aag gac   48
Met Pro Phe Pro Gly Pro His Ala Gly Arg Ser Ser Thr Leu Lys Asp
  1               5                  10                  15

acc acc cct cca tcc cac caa ata ttt gga agg ctc ctg gaa gat ctc   96
Thr Thr Pro Pro Ser His Gln Ile Phe Gly Arg Leu Leu Glu Asp Leu
             20                  25                  30

caa atc caa gtg tct ccc act gcc cac ggc att cca gac act ttt gac   144
Gln Ile Gln Val Ser Pro Thr Ala His Gly Ile Pro Asp Thr Phe Asp
         35                  40                  45

cct tac ctg gac atc gcc ctg gat atc cag gca gct cag agt gtc cag   192
Pro Tyr Leu Asp Ile Ala Leu Asp Ile Gln Ala Ala Gln Ser Val Gln
     50                  55                  60

caa gct ttg gaa cag ttg gtg aag ccc gaa gaa ctc aat gga gag aat   240
Gln Ala Leu Glu Gln Leu Val Lys Pro Glu Glu Leu Asn Gly Glu Asn
 65                  70                  75                  80

gcc tat cat tgt ggt ctt tgt ctc cag agg gcg ccg gcc tcc aag acg   288
Ala Tyr His Cys Gly Leu Cys Leu Gln Arg Ala Pro Ala Ser Lys Thr
                 85                  90                  95

tta act tta cac acc tct gcc aag gtc ctc atc ctt gtc ttg aag aga   336
Leu Thr Leu His Thr Ser Ala Lys Val Leu Ile Leu Val Leu Lys Arg
            100                 105                 110

ttc tcc gat gtc aca ggc aac aag att gcc aag aat gtg caa tat cct   384
Phe Ser Asp Val Thr Gly Asn Lys Ile Ala Lys Asn Val Gln Tyr Pro
        115                 120                 125
```

```
gag tgc ctt gac atg cag cca tac atg tct cag cag aac aca gga cct   432
Glu Cys Leu Asp Met Gln Pro Tyr Met Ser Gln Gln Asn Thr Gly Pro
    130                 135                 140

ctt gtc tat gtc ctc tat gct gtg ctg gtc cac gct ggg tgg agt tgt   480
Leu Val Tyr Val Leu Tyr Ala Val Leu Val His Ala Gly Trp Ser Cys
145                 150                 155                 160

cac aac gga cat tac ttc tct tat gtc aaa gct caa gaa ggc cag tgg   528
His Asn Gly His Tyr Phe Ser Tyr Val Lys Ala Gln Glu Gly Gln Trp
                165                 170                 175

tat aaa atg gat gat gcc gag gtc acc gcc tct agc atc act tct gtc   576
Tyr Lys Met Asp Asp Ala Glu Val Thr Ala Ser Ser Ile Thr Ser Val
            180                 185                 190

ctg agt caa cag gcc tac gtc ctc ttt tac atc cag aag agt gaa tgg   624
Leu Ser Gln Gln Ala Tyr Val Leu Phe Tyr Ile Gln Lys Ser Glu Trp
        195                 200                 205

gaa aga cac agt gag agt gtg tca aga ggc agg gaa cca aga gcc ctt   672
Glu Arg His Ser Glu Ser Val Ser Arg Gly Arg Glu Pro Arg Ala Leu
    210                 215                 220

ggc gca gaa gac aca gac agg cga gca acg caa gga gag ctc aag aga   720
Gly Ala Glu Asp Thr Asp Arg Arg Ala Thr Gln Gly Glu Leu Lys Arg
225                 230                 235                 240

gac cac ccc tgc ctc cag gcc ccc gag ttg gac gag cac ttg gtg gaa   768
Asp His Pro Cys Leu Gln Ala Pro Glu Leu Asp Glu His Leu Val Glu
                245                 250                 255

aga gcc act cag gaa agc acc tta gac cac tgg aaa ttc ctt caa gag   816
Arg Ala Thr Gln Glu Ser Thr Leu Asp His Trp Lys Phe Leu Gln Glu
            260                 265                 270

caa aac aaa acg aag cct gag ttc aac gtc aga aaa gtc gaa ggt acc   864
Gln Asn Lys Thr Lys Pro Glu Phe Asn Val Arg Lys Val Glu Gly Thr
        275                 280                 285

ctg cct ccc gac gta ctt gtg att cat caa tca aaa tac aag tgt ggg   912
Leu Pro Pro Asp Val Leu Val Ile His Gln Ser Lys Tyr Lys Cys Gly
    290                 295                 300

atg aag aac cat cat cct gaa cag caa agc tcc ctg cta aac ctc tct   960
Met Lys Asn His His Pro Glu Gln Gln Ser Ser Leu Leu Asn Leu Ser
305                 310                 315                 320

tcg acg acc ccg aca cat cag gag tcc atg aac act ggc aca ctc gct  1008
Ser Thr Thr Pro Thr His Gln Glu Ser Met Asn Thr Gly Thr Leu Ala
                325                 330                 335

tcc ctg cga ggg agg gcc agg aga tcc aaa ggg aag aac aaa cac agc  1056
Ser Leu Arg Gly Arg Ala Arg Arg Ser Lys Gly Lys Asn Lys His Ser
            340                 345                 350

aag agg gct ctg ctt gtg tgc cag tg                              1082
Lys Arg Ala Leu Leu Val Cys Gln
        355                 360
```

<210> 32
<211> 360
<212> PRT
<213> Unknown

<400> 32

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Met Pro Phe Pro Gly Pro His Ala Gly Arg Ser Ser Thr Leu Lys Asp
 1               5                  10                  15

Thr Thr Pro Pro Ser His Gln Ile Phe Gly Arg Leu Leu Glu Asp Leu
            20                  25                  30

Gln Ile Gln Val Ser Pro Thr Ala His Gly Ile Pro Asp Thr Phe Asp
        35                  40                  45

Pro Tyr Leu Asp Ile Ala Leu Asp Ile Gln Ala Ala Gln Ser Val Gln
    50                  55                  60

Gln Ala Leu Glu Gln Leu Val Lys Pro Glu Glu Leu Asn Gly Glu Asn
65                  70                  75                  80

Ala Tyr His Cys Gly Leu Cys Leu Gln Arg Ala Pro Ala Ser Lys Thr
                85                  90                  95

Leu Thr Leu His Thr Ser Ala Lys Val Leu Ile Leu Val Leu Lys Arg
            100                 105                 110

Phe Ser Asp Val Thr Gly Asn Lys Ile Ala Lys Asn Val Gln Tyr Pro
        115                 120                 125

Glu Cys Leu Asp Met Gln Pro Tyr Met Ser Gln Gln Asn Thr Gly Pro
    130                 135                 140

Leu Val Tyr Val Leu Tyr Ala Val Leu Val His Ala Gly Trp Ser Cys
145                 150                 155                 160

His Asn Gly His Tyr Phe Ser Tyr Val Lys Ala Gln Glu Gly Gln Trp
                165                 170                 175

Tyr Lys Met Asp Asp Ala Glu Val Thr Ala Ser Ser Ile Thr Ser Val
            180                 185                 190

Leu Ser Gln Gln Ala Tyr Val Leu Phe Tyr Ile Gln Lys Ser Glu Trp
        195                 200                 205

Glu Arg His Ser Glu Ser Val Ser Arg Gly Arg Glu Pro Arg Ala Leu
    210                 215                 220

Gly Ala Glu Asp Thr Asp Arg Arg Ala Thr Gln Gly Glu Leu Lys Arg
225                 230                 235                 240

Asp His Pro Cys Leu Gln Ala Pro Glu Leu Asp Glu His Leu Val Glu
                245                 250                 255

Arg Ala Thr Gln Glu Ser Thr Leu Asp His Trp Lys Phe Leu Gln Glu
            260                 265                 270

Gln Asn Lys Thr Lys Pro Glu Phe Asn Val Arg Lys Val Glu Gly Thr
        275                 280                 285
```

```
Leu Pro Pro Asp Val Leu Val Ile His Gln Ser Lys Tyr Lys Cys Gly
290                 295                 300

Met Lys Asn His His Pro Glu Gln Gln Ser Ser Leu Leu Asn Leu Ser
305                 310                 315                 320

Ser Thr Thr Pro Thr His Gln Glu Ser Met Asn Thr Gly Thr Leu Ala
                325                 330                 335

Ser Leu Arg Gly Arg Ala Arg Arg Ser Lys Gly Lys Asn Lys His Ser
            340                 345                 350

Lys Arg Ala Leu Leu Val Cys Gln
        355                 360
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<210> 33
<211> 1683
<212> DNA
<213> Unknown

<220>
<223> Description of Unknown Organism:primate

<220>
<221> CDS
<222> (1)..(1590)

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<400> 33
atg gag gac gac tca ctc tac ttg gga ggt gag tgg cag ttc aac cac   48
Met Glu Asp Asp Ser Leu Tyr Leu Gly Gly Glu Trp Gln Phe Asn His
 1               5                  10                  15

ttt tca aaa ctc aca tct tct cgg cca gat gca gct ttt gct gaa atc   96
Phe Ser Lys Leu Thr Ser Ser Arg Pro Asp Ala Ala Phe Ala Glu Ile
            20                  25                  30

cag cgg act tct ctc cct gag aag tca cca ctc tca tct gag gcc cgt  144
Gln Arg Thr Ser Leu Pro Glu Lys Ser Pro Leu Ser Ser Glu Ala Arg
        35                  40                  45

gtc gac ctc tgt gat gat ttg gct cct gtg gca aga cag ctt gct ccc  192
Val Asp Leu Cys Asp Asp Leu Ala Pro Val Ala Arg Gln Leu Ala Pro
    50                  55                  60

agg gag aag ctt cct ctg agt agc agg aga cct gct gcg gtg ggg gct  240
Arg Glu Lys Leu Pro Leu Ser Ser Arg Arg Pro Ala Ala Val Gly Ala
65                  70                  75                  80

ggg ctc cag aat atg gga aat acc tgc tac gag aac gct tcc ctg cag  288
Gly Leu Gln Asn Met Gly Asn Thr Cys Tyr Glu Asn Ala Ser Leu Gln
                85                  90                  95

tgc ctg aca tac aca ccg ccc ctt gcc aac tac atg ctg tcc cgg gag  336
Cys Leu Thr Tyr Thr Pro Pro Leu Ala Asn Tyr Met Leu Ser Arg Glu
            100                 105                 110

cac tct caa aca tgt cag cgt ccc aag tgc tgc atg ctc tgt act atg  384
His Ser Gln Thr Cys Gln Arg Pro Lys Cys Cys Met Leu Cys Thr Met
        115                 120                 125
```

```
caa gct cac atc aca tgg gcc ctc cac agt cct ggt cat gtc atc cag  432
Gln Ala His Ile Thr Trp Ala Leu His Ser Pro Gly His Val Ile Gln
    130                 135                 140

ccc tca cag gca ttg gct gct ggc ttc cat aga ggc aag cag gaa gat  480
Pro Ser Gln Ala Leu Ala Ala Gly Phe His Arg Gly Lys Gln Glu Asp
145                 150                 155                 160

gcc cat gaa ttt ctc atg ttc act gtg gat gcc atg aaa aag gca tgc  528
Ala His Glu Phe Leu Met Phe Thr Val Asp Ala Met Lys Lys Ala Cys
                165                 170                 175

ctt ccc ggc cac aag cag gta gat cat cac tct aag gac acc acc ctc  576
Leu Pro Gly His Lys Gln Val Asp His His Ser Lys Asp Thr Thr Leu
            180                 185                 190

atc cac caa ata ttt gga ggc tgc tgg aga tct caa atc aag tgt ctc  624
Ile His Gln Ile Phe Gly Gly Cys Trp Arg Ser Gln Ile Lys Cys Leu
        195                 200                 205

cac tgc cac ggg att cca gac act ttt gac cct tac ctg gac atc gcc  672
His Cys His Gly Ile Pro Asp Thr Phe Asp Pro Tyr Leu Asp Ile Ala
    210                 215                 220

ctg gat atc cag gca gct cag agt gtc aag caa gct ttg gaa cag ttg  720
Leu Asp Ile Gln Ala Ala Gln Ser Val Lys Gln Ala Leu Glu Gln Leu
225                 230                 235                 240

gtg aag ccc gaa gaa ctc aat gga gag aat gcc tat cat tgt ggt ctt  768
Val Lys Pro Glu Glu Leu Asn Gly Glu Asn Ala Tyr His Cys Gly Leu
                245                 250                 255

tgt ctc cag agg gcg ccg gcc tcc aag acg tta act tta cac act tct  816
Cys Leu Gln Arg Ala Pro Ala Ser Lys Thr Leu Thr Leu His Thr Ser
            260                 265                 270

gcc aag gtc ctc atc ctt gtm ttg aag aga ttc tcc gat gtc aca ggc  864
Ala Lys Val Leu Ile Leu Xaa Leu Lys Arg Phe Ser Asp Val Thr Gly
        275                 280                 285

aac aaa ctt gcc aag aat gtg caa tat cct gag tgc ctt gac atg cag  912
Asn Lys Leu Ala Lys Asn Val Gln Tyr Pro Glu Cys Leu Asp Met Gln
    290                 295                 300

cca tac atg tct cag cag aac aca gga cct ctt gtc tat gtc ctc tat  960
Pro Tyr Met Ser Gln Gln Asn Thr Gly Pro Leu Val Tyr Val Leu Tyr
305                 310                 315                 320

gct gtg ctg gtc cac gct ggg tgg agt tgt cac aac gga cat tac ttc 1008
Ala Val Leu Val His Ala Gly Trp Ser Cys His Asn Gly His Tyr Phe
                325                 330                 335

tct tat gtc aaa gct caa gaa ggc cag tgg tat aaa atg gat gat gcc 1056
Ser Tyr Val Lys Ala Gln Glu Gly Gln Trp Tyr Lys Met Asp Asp Ala
            340                 345                 350

gag gtc acc gcc tct agc atc act tct gtc ctg agt caa cag gcc tac 1104
Glu Val Thr Ala Ser Ser Ile Thr Ser Val Leu Ser Gln Gln Ala Tyr
        355                 360                 365
```

```
gtc ctc ttt tac atc cag aag agt gaa tgg gaa aga cac agt gag agt   1152
Val Leu Phe Tyr Ile Gln Lys Ser Glu Trp Glu Arg His Ser Glu Ser
    370                 375                 380

gtg tca aga ggc agg gaa cca aga gcc ctt ggc gca gaa gac aca gac   1200
Val Ser Arg Gly Arg Glu Pro Arg Ala Leu Gly Ala Glu Asp Thr Asp
385                 390                 395                 400

agg cga gca acg caa gga gag ctc aag aga gac cac ccc tgc ctc cag   1248
Arg Arg Ala Thr Gln Gly Glu Leu Lys Arg Asp His Pro Cys Leu Gln
                405                 410                 415

gcc ccc gag ttg gac gag cac ttg gtg gaa aga gcc act cag gaa agc   1296
Ala Pro Glu Leu Asp Glu His Leu Val Glu Arg Ala Thr Gln Glu Ser
            420                 425                 430

acc tta gac cac tgg aaa ttc ctt caa gag caa aac aaa acg aag cct   1344
Thr Leu Asp His Trp Lys Phe Leu Gln Glu Gln Asn Lys Thr Lys Pro
        435                 440                 445

gag ttc aac gtc aga aaa gtc gaa ggt acc ctg cct ccc gac gta ctt   1392
Glu Phe Asn Val Arg Lys Val Glu Gly Thr Leu Pro Pro Asp Val Leu
    450                 455                 460

gtg att cat caa tca aaa tac aag tgt ggg atg aag aac cat cat cct   1440
Val Ile His Gln Ser Lys Tyr Lys Cys Gly Met Lys Asn His His Pro
465                 470                 475                 480

gaa cag caa agc tcc ctg cta aac ctc tct tcg acg acc ccg aca cat   1488
Glu Gln Gln Ser Ser Leu Leu Asn Leu Ser Ser Thr Thr Pro Thr His
                485                 490                 495

cag gag tcc atg aac act ggc aca ctc gct tcc ctg cga ggg agg gcc   1536
Gln Glu Ser Met Asn Thr Gly Thr Leu Ala Ser Leu Arg Gly Arg Ala
            500                 505                 510

agg aga tcc aaa ggg aag aac aaa cac agc aag agg gct ctg ctt gtg   1584
Arg Arg Ser Lys Gly Lys Asn Lys His Ser Lys Arg Ala Leu Leu Val
        515                 520                 525

tgc cag tgatctcagt ggaagtaccg acccacacgt aggggtgcac acacacacgc   1640
Cys Gln
    530

acacacacag acacacacat aactacaccc agaagcgcgc tga                  1683
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<210> 34
<211> 530
<212> PRT
<213> Unknown

<400> 34

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Met Glu Asp Asp Ser Leu Tyr Leu Gly Gly Glu Trp Gln Phe Asn His
  1               5                  10                  15

Phe Ser Lys Leu Thr Ser Ser Arg Pro Asp Ala Ala Phe Ala Glu Ile
             20                  25                  30

Gln Arg Thr Ser Leu Pro Glu Lys Ser Pro Leu Ser Ser Glu Ala Arg
         35                  40                  45
```

```
Val Asp Leu Cys Asp Asp Leu Ala Pro Val Ala Arg Gln Leu Ala Pro
     50                  55                  60

Arg Glu Lys Leu Pro Leu Ser Ser Arg Arg Pro Ala Ala Val Gly Ala
 65                  70                  75                  80

Gly Leu Gln Asn Met Gly Asn Thr Cys Tyr Glu Asn Ala Ser Leu Gln
                 85                  90                  95

Cys Leu Thr Tyr Thr Pro Pro Leu Ala Asn Tyr Met Leu Ser Arg Glu
            100                 105                 110

His Ser Gln Thr Cys Gln Arg Pro Lys Cys Cys Met Leu Cys Thr Met
        115                 120                 125

Gln Ala His Ile Thr Trp Ala Leu His Ser Pro Gly His Val Ile Gln
    130                 135                 140

Pro Ser Gln Ala Leu Ala Ala Gly Phe His Arg Gly Lys Gln Glu Asp
145                 150                 155                 160

Ala His Glu Phe Leu Met Phe Thr Val Asp Ala Met Lys Lys Ala Cys
                165                 170                 175

Leu Pro Gly His Lys Gln Val Asp His His Ser Lys Asp Thr Thr Leu
            180                 185                 190

Ile His Gln Ile Phe Gly Gly Cys Trp Arg Ser Gln Ile Lys Cys Leu
        195                 200                 205

His Cys His Gly Ile Pro Asp Thr Phe Asp Pro Tyr Leu Asp Ile Ala
    210                 215                 220

Leu Asp Ile Gln Ala Ala Gln Ser Val Lys Gln Ala Leu Glu Gln Leu
225                 230                 235                 240

Val Lys Pro Glu Glu Leu Asn Gly Glu Asn Ala Tyr His Cys Gly Leu
                245                 250                 255

Cys Leu Gln Arg Ala Pro Ala Ser Lys Thr Leu Thr Leu His Thr Ser
            260                 265                 270

Ala Lys Val Leu Ile Leu Xaa Leu Lys Arg Phe Ser Asp Val Thr Gly
        275                 280                 285

Asn Lys Leu Ala Lys Asn Val Gln Tyr Pro Glu Cys Leu Asp Met Gln
    290                 295                 300

Pro Tyr Met Ser Gln Gln Asn Thr Gly Pro Leu Val Tyr Val Leu Tyr
305                 310                 315                 320

Ala Val Leu Val His Ala Gly Trp Ser Cys His Asn Gly His Tyr Phe
                325                 330                 335

Ser Tyr Val Lys Ala Gln Glu Gly Gln Trp Tyr Lys Met Asp Asp Ala
            340                 345                 350

Glu Val Thr Ala Ser Ser Ile Thr Ser Val Leu Ser Gln Gln Ala Tyr
        355                 360                 365
```

Val Leu Phe Tyr Ile Gln Lys Ser Glu Trp Glu Arg His Ser Glu Ser
370 375 380

Val Ser Arg Gly Arg Glu Pro Arg Ala Leu Gly Ala Glu Asp Thr Asp
385 390 395 400

Arg Arg Ala Thr Gln Gly Glu Leu Lys Arg Asp His Pro Cys Leu Gln
405 410 415

Ala Pro Glu Leu Asp Glu His Leu Val Glu Arg Ala Thr Gln Glu Ser
420 425 430

Thr Leu Asp His Trp Lys Phe Leu Gln Glu Gln Asn Lys Thr Lys Pro
435 440 445

Glu Phe Asn Val Arg Lys Val Glu Gly Thr Leu Pro Pro Asp Val Leu
450 455 460

Val Ile His Gln Ser Lys Tyr Lys Cys Gly Met Lys Asn His His Pro
465 470 475 480

Glu Gln Gln Ser Ser Leu Leu Asn Leu Ser Ser Thr Thr Pro Thr His
485 490 495

Gln Glu Ser Met Asn Thr Gly Thr Leu Ala Ser Leu Arg Gly Arg Ala
500 505 510

Arg Arg Ser Lys Gly Lys Asn Lys His Ser Lys Arg Ala Leu Leu Val
515 520 525

Cys Gln
530

<210> 35
<211> 735
<212> DNA
<213> Unknown

<220>
<223> Description of Unknown Organism:primate

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<221> CDS
<222> (1)..(735)

<220>
<221> misc_feature
<222> (197)
<223> nucleotide may be A or C

<220>
<221> misc_feature
<222> (590)
<223> nucleotide may be A, C, G, or T

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<221> misc_feature
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<223> nucleotide may be A, C, G, or T

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<221> misc_feature
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<223> nucleotide may be A, C, G, or T

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<221> misc_feature
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<220>
<221> misc_feature
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<223> nucleotide may be A, C, G, or T

<220>
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<223> nucleotide may be A, C, G, or T

<400> 35

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atg gct gtg cca agt tgg atc gtc aaa cgc agg cta cta cct tgg tcc   48
Met Ala Val Pro Ser Trp Ile Val Lys Arg Arg Leu Leu Pro Trp Ser
  1               5                  10                  15

atc aaa ttt ttg gag ggt atc tca gat cac ggc gtg aag tgc tcc gtg   96
Ile Lys Phe Leu Glu Gly Ile Ser Asp His Gly Val Lys Cys Ser Val
             20                  25                  30

tgc aag agc gtc tcg gac acc tac gac ccc tac ttg gac gtc gcg ctg   144
Cys Lys Ser Val Ser Asp Thr Tyr Asp Pro Tyr Leu Asp Val Ala Leu
          35                  40                  45

gag atc cgg caa gct gcg aat att gtg cgt gct ctg gaa ctt ttt gtg   192
Glu Ile Arg Gln Ala Ala Asn Ile Val Arg Ala Leu Glu Leu Phe Val
      50                  55                  60

aaa gca gat gtc ctg agt gga gag aat gcc tac atg tgt gct aaa tgc   240
Lys Ala Asp Val Leu Ser Gly Glu Asn Ala Tyr Met Cys Ala Lys Cys
  65                  70                  75                  80

aag aag aag gtt cca gcc agc aag cgc ttc acc atc cac aga aca tcc   288
Lys Lys Lys Val Pro Ala Ser Lys Arg Phe Thr Ile His Arg Thr Ser
                 85                  90                  95

aac gtc tta acc ctt tcc ctc aag cgc ttt gcc aac ttc agc ggg ggg   336
Asn Val Leu Thr Leu Ser Leu Lys Arg Phe Ala Asn Phe Ser Gly Gly
            100                 105                 110

aag atc acc aag gat gta ggc tat ccg gaa ttc ctc aac ata cgt ccg   384
Lys Ile Thr Lys Asp Val Gly Tyr Pro Glu Phe Leu Asn Ile Arg Pro
        115                 120                 125

tat atg tcc cag aat aat ggt gat cct gtc atg tat gga ctc tat gct   432
Tyr Met Ser Gln Asn Asn Gly Asp Pro Val Met Tyr Gly Leu Tyr Ala
    130                 135                 140

gtc ctg gtg cac tcg ggc tac agc tgc cat gcc ggg cac tat tac tgc   480
Val Leu Val His Ser Gly Tyr Ser Cys His Ala Gly His Tyr Tyr Cys
145                 150                 155                 160
```

```
tac gtg aag gca agc aat gga cag tgg tac cag atg aat gat tcc ttg   528
Tyr Val Lys Ala Ser Asn Gly Gln Trp Tyr Gln Met Asn Asp Ser Leu
                165                 170                 175

gtc cca ttc cag caa cgt cca agt tgg ttt ctg aaa cca gca ggc cta   576
Val Pro Phe Gln Gln Arg Pro Ser Trp Phe Leu Lys Pro Ala Gly Leu
            180                 185                 190

agt ggc ttg ttc tca tcg gcg aat ttc cag gct ctc aag aaa aat tcc   624
Ser Gly Leu Phe Ser Ser Ala Asn Phe Gln Ala Leu Lys Lys Asn Ser
        195                 200                 205

cga agg gcc tcc att ttc cag gaa cag gtt cct tcc tcc cct tcc cgg   672
Arg Arg Ala Ser Ile Phe Gln Glu Gln Val Pro Ser Ser Pro Ser Arg
    210                 215                 220

gcg gcc cga att gtg aat tcc aga ttc att ccc agc agg aac ctc ggc   720
Ala Ala Arg Ile Val Asn Ser Arg Phe Ile Pro Ser Arg Asn Leu Gly
225                 230                 235                 240

aat ggg gat tat ttt                                              735
Asn Gly Asp Tyr Phe
                245
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<210> 36
<211> 245
<212> PRT
<213> Unknown

<400> 36

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Met Ala Val Pro Ser Trp Ile Val Lys Arg Arg Leu Leu Pro Trp Ser
  1               5                  10                  15

Ile Lys Phe Leu Glu Gly Ile Ser Asp His Gly Val Lys Cys Ser Val
            20                  25                  30

Cys Lys Ser Val Ser Asp Thr Tyr Asp Pro Tyr Leu Asp Val Ala Leu
        35                  40                  45

Glu Ile Arg Gln Ala Ala Asn Ile Val Arg Ala Leu Glu Leu Phe Val
    50                  55                  60

Lys Ala Asp Val Leu Ser Gly Glu Asn Ala Tyr Met Cys Ala Lys Cys
65                  70                  75                  80

Lys Lys Lys Val Pro Ala Ser Lys Arg Phe Thr Ile His Arg Thr Ser
                85                  90                  95

Asn Val Leu Thr Leu Ser Leu Lys Arg Phe Ala Asn Phe Ser Gly Gly
            100                 105                 110

Lys Ile Thr Lys Asp Val Gly Tyr Pro Glu Phe Leu Asn Ile Arg Pro
        115                 120                 125

Tyr Met Ser Gln Asn Asn Gly Asp Pro Val Met Tyr Gly Leu Tyr Ala
    130                 135                 140

Val Leu Val His Ser Gly Tyr Ser Cys His Ala Gly His Tyr Tyr Cys
145                 150                 155                 160
```

```
Tyr Val Lys Ala Ser Asn Gly Gln Trp Tyr Gln Met Asn Asp Ser Leu
                165                 170                 175

Val Pro Phe Gln Gln Arg Pro Ser Trp Phe Leu Lys Pro Ala Gly Leu
            180                 185                 190

Ser Gly Leu Phe Ser Ser Ala Asn Phe Gln Ala Leu Lys Lys Asn Ser
        195                 200                 205

Arg Arg Ala Ser Ile Phe Gln Glu Gln Val Pro Ser Ser Pro Ser Arg
    210                 215                 220

Ala Ala Arg Ile Val Asn Ser Arg Phe Ile Pro Ser Arg Asn Leu Gly
225                 230                 235                 240

Asn Gly Asp Tyr Phe
                245
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<210> 37
<211> 2244
<212> DNA
<213> Unknown

<220>
<223> Description of Unknown Organism:primate

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<221> CDS
<222> (1)..(2244)

<400> 37

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atg cag aaa gcc tgc ctg aat ggc tgt gcc aag ttg gat cgt caa acg   48
Met Gln Lys Ala Cys Leu Asn Gly Cys Ala Lys Leu Asp Arg Gln Thr
  1               5                  10                  15

cag gct act acc ttg gtc cat caa att ttt gga ggg tat ctc aga tca   96
Gln Ala Thr Thr Leu Val His Gln Ile Phe Gly Gly Tyr Leu Arg Ser
             20                  25                  30

cgc gtg aag tgc tcc gtg tgc aag agc gtc tcg gac acc tac gac ccc   144
Arg Val Lys Cys Ser Val Cys Lys Ser Val Ser Asp Thr Tyr Asp Pro
          35                  40                  45

tac ttg gac gtc gcg ctg gag atc cgg caa gct gcg aat att gtg cgt   192
Tyr Leu Asp Val Ala Leu Glu Ile Arg Gln Ala Ala Asn Ile Val Arg
      50                  55                  60

gct ctg gaa ctt ttt gtg aaa gca gat gtc ctg agt gga gag aat gcc   240
Ala Leu Glu Leu Phe Val Lys Ala Asp Val Leu Ser Gly Glu Asn Ala
  65                  70                  75                  80

tac atg tgt gct aaa tgc aag aag aag gtt cca gcc agc aag cgc ttc   288
Tyr Met Cys Ala Lys Cys Lys Lys Lys Val Pro Ala Ser Lys Arg Phe
                85                  90                  95

acc atc cac aga aca tcc aac gtc tta acc ctt tcc ctc aag cgc ttt   336
Thr Ile His Arg Thr Ser Asn Val Leu Thr Leu Ser Leu Lys Arg Phe
            100                 105                 110

gcc aac ttc agc ggg ggg aag atc acc aag gat gta ggc tat ccg gaa   384
```

```
Ala Asn Phe Ser Gly Gly Lys Ile Thr Lys Asp Val Gly Tyr Pro Glu
        115                 120                 125

ttc ctc aac ata cgt ccg tat atg tcc cag aat aat ggt gat cct gtc   432
Phe Leu Asn Ile Arg Pro Tyr Met Ser Gln Asn Asn Gly Asp Pro Val
    130                 135                 140

atg tat gga ctc tat gct gtc ctg gtg cac tcg ggc tac agc tgc cat   480
Met Tyr Gly Leu Tyr Ala Val Leu Val His Ser Gly Tyr Ser Cys His
145                 150                 155                 160

gcc ggg cac tat tac tgc tac gtg aag gca agc aat gga cag tgg tac   528
Ala Gly His Tyr Tyr Cys Tyr Val Lys Ala Ser Asn Gly Gln Trp Tyr
                165                 170                 175

cag atg aat gat tcc ttg gtc cat tcc agc aac gtc aag gtg gtt ctg   576
Gln Met Asn Asp Ser Leu Val His Ser Ser Asn Val Lys Val Val Leu
            180                 185                 190

aac cag cag gcc tac gtg ctg ttc tat ctg cga att cca ggc tct aag   624
Asn Gln Gln Ala Tyr Val Leu Phe Tyr Leu Arg Ile Pro Gly Ser Lys
        195                 200                 205

aaa agt ccc gag ggc ctc atc tcc agg aca ggc tcc tcc tcc ctt ccc   672
Lys Ser Pro Glu Gly Leu Ile Ser Arg Thr Gly Ser Ser Ser Leu Pro
    210                 215                 220

ggc cgc ccg agt gtg att cca gat cac tcc aag aag aac atc ggc aat   720
Gly Arg Pro Ser Val Ile Pro Asp His Ser Lys Lys Asn Ile Gly Asn
225                 230                 235                 240

ggg att att tcc tcc cca ctg act gga aag cga caa gac tct ggg acg   768
Gly Ile Ile Ser Ser Pro Leu Thr Gly Lys Arg Gln Asp Ser Gly Thr
                245                 250                 255

atg aag aag ccg cac acc act gaa gag att ggt gtg ccc ata tcc agg   816
Met Lys Lys Pro His Thr Thr Glu Glu Ile Gly Val Pro Ile Ser Arg
            260                 265                 270

aat ggc tcc acc ctg ggc ctg aag tcc cag aac ggc tgc att cct cca   864
Asn Gly Ser Thr Leu Gly Leu Lys Ser Gln Asn Gly Cys Ile Pro Pro
        275                 280                 285

aag ctg ccc tcg ggg tcc cct tcc ccc aaa ctc tcc cag aca ccc aca   912
Lys Leu Pro Ser Gly Ser Pro Ser Pro Lys Leu Ser Gln Thr Pro Thr
    290                 295                 300

cac atg cca acc atc cta gac gac cct gga aag aag gtg aag aag cca   960
His Met Pro Thr Ile Leu Asp Asp Pro Gly Lys Lys Val Lys Lys Pro
305                 310                 315                 320

gct cct cca cag cac ttt tcc ccc aga act gct cag ggg ctg cct ggg  1008
Ala Pro Pro Gln His Phe Ser Pro Arg Thr Ala Gln Gly Leu Pro Gly
                325                 330                 335

acc agc aac tcg aat agc agc aga tct ggg agc caa agg cag ggc tcc  1056
Thr Ser Asn Ser Asn Ser Ser Arg Ser Gly Ser Gln Arg Gln Gly Ser
            340                 345                 350

tgg gac agc agg gat gtt gtc ctc tct acc tca cct aag ctc ctg gct  1104
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```
     Trp Asp Ser Arg Asp Val Val Leu Ser Thr Ser Pro Lys Leu Leu Ala
 5           355                 360                 365

     aca gcc act gcc aac ggg cat ggg ctg aag ggg aac gac gag agc gct   1152
     Thr Ala Thr Ala Asn Gly His Gly Leu Lys Gly Asn Asp Glu Ser Ala
         370                 375                 380
10
     ggc ctc gac agg agg ggc tcc agc agc tcc agc cca gag cac tcg gcc   1200
     Gly Leu Asp Arg Arg Gly Ser Ser Ser Ser Ser Pro Glu His Ser Ala
     385                 390                 395                 400

15   agc agc gac tcc acc aag gcc ccc cag acc ccc agg agt gga gcg gcc   1248
     Ser Ser Asp Ser Thr Lys Ala Pro Gln Thr Pro Arg Ser Gly Ala Ala
                     405                 410                 415

     cat ctc tgc gat tct cag gaa acg aac tgt tcc acc gct ggc cac tcc   1296
20   His Leu Cys Asp Ser Gln Glu Thr Asn Cys Ser Thr Ala Gly His Ser
                 420                 425                 430

     aaa acg ccg cca agt gga gca gat tct aag acg gtg aag ctg aag tcc   1344
     Lys Thr Pro Pro Ser Gly Ala Asp Ser Lys Thr Val Lys Leu Lys Ser
25           435                 440                 445

     cct gtc ctg agc aac acc acc act gag cct gca agc acc atg tct cct   1392
     Pro Val Leu Ser Asn Thr Thr Thr Glu Pro Ala Ser Thr Met Ser Pro
         450                 455                 460
30
     cca cca gcc aaa aaa ctg gcc ctt tct gcc aag aag gcc agc acc ctg   1440
     Pro Pro Ala Lys Lys Leu Ala Leu Ser Ala Lys Lys Ala Ser Thr Leu
     465                 470                 475                 480

35   tgg agg gcg acc ggc aat gac ctc cgt cca cct ccc ccc tca cca tcc   1488
     Trp Arg Ala Thr Gly Asn Asp Leu Arg Pro Pro Pro Pro Ser Pro Ser
                     485                 490                 495

     tcc gac ctc acc cac ccc atg aaa acc tct cac ccc gtc gtt gcc tcc   1536
40   Ser Asp Leu Thr His Pro Met Lys Thr Ser His Pro Val Val Ala Ser
                 500                 505                 510

     act tgg ccc gtc cat aga gcc agg gct gtg tca cct gct ccc caa tca   1584
     Thr Trp Pro Val His Arg Ala Arg Ala Val Ser Pro Ala Pro Gln Ser
45           515                 520                 525

     tcc agc cgc ctg caa ccc ccc ttc agc ccc cac ccc aca ttg ctg tcc   1632
     Ser Ser Arg Leu Gln Pro Pro Phe Ser Pro His Pro Thr Leu Leu Ser
         530                 535                 540
50
     agt acc ccc aag ccc cca ggg acg tca gaa cca cgg agc tgc tcc tcc   1680
     Ser Thr Pro Lys Pro Pro Gly Thr Ser Glu Pro Arg Ser Cys Ser Ser
     545                 550                 555                 560

55   atc tcg acg gcg ctg cct cag gtc aac gag gac ctt gtg tct ctt cca   1728
     Ile Ser Thr Ala Leu Pro Gln Val Asn Glu Asp Leu Val Ser Leu Pro
                     565                 570                 575

     cac cag ttg cca gag gcc agt gag ccc ccc cag agc ccc tct gag aag   1776
60   His Gln Leu Pro Glu Ala Ser Glu Pro Pro Gln Ser Pro Ser Glu Lys
                 580                 585                 590
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```
agg aaa aag acc ttt gtg gga gag ccg cag agg ctg ggc tca gag acg   1824
Arg Lys Lys Thr Phe Val Gly Glu Pro Gln Arg Leu Gly Ser Glu Thr
        595                 600                 605

cgc ctc cca cag cac atc agg gag gcc act gcg gct ccc cac ggg aag   1872
Arg Leu Pro Gln His Ile Arg Glu Ala Thr Ala Ala Pro His Gly Lys
    610                 615                 620

agg aag agg aag aag aag aag cgc ccg gag gac aca gct gcc agc gcc   1920
Arg Lys Arg Lys Lys Lys Lys Arg Pro Glu Asp Thr Ala Ala Ser Ala
625                 630                 635                 640

ctg cag gag ggg cag aca cag aga cag cct ggg agc ccc atg tac agg   1968
Leu Gln Glu Gly Gln Thr Gln Arg Gln Pro Gly Ser Pro Met Tyr Arg
                645                 650                 655

agg gag ggc cag gca cag ctg ccc gct gtc aga cgg cag gaa gat ggc   2016
Arg Glu Gly Gln Ala Gln Leu Pro Ala Val Arg Arg Gln Glu Asp Gly
            660                 665                 670

aca cag cca cag gtg aat ggc cag cag gtg gga tgt gtt acg gac ggc   2064
Thr Gln Pro Gln Val Asn Gly Gln Gln Val Gly Cys Val Thr Asp Gly
        675                 680                 685

cac cac gcg agc agc agg aag cgg agg agg aaa gga gca gaa ggt ctt   2112
His His Ala Ser Ser Arg Lys Arg Arg Arg Lys Gly Ala Glu Gly Leu
    690                 695                 700

ggt gaa gaa ggc ggc ctg cac cag gac cca ctt cgg cac agc tgc tct   2160
Gly Glu Glu Gly Gly Leu His Gln Asp Pro Leu Arg His Ser Cys Ser
705                 710                 715                 720

ccc atg ggt gat ggt gat cca gag gcc atg gaa gag tct cca agg aaa   2208
Pro Met Gly Asp Gly Asp Pro Glu Ala Met Glu Glu Ser Pro Arg Lys
                725                 730                 735

aag aaa aaa aaa aaa aac tcg agg ggg ggc ccg gta                   2244
Lys Lys Lys Lys Lys Asn Ser Arg Gly Gly Pro Val
            740                 745
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<210> 38
<211> 748
<212> PRT
<213> Unknown

<400> 38

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Met Gln Lys Ala Cys Leu Asn Gly Cys Ala Lys Leu Asp Arg Gln Thr
  1               5                  10                  15

Gln Ala Thr Thr Leu Val His Gln Ile Phe Gly Gly Tyr Leu Arg Ser
            20                  25                  30

Arg Val Lys Cys Ser Val Cys Lys Ser Val Ser Asp Thr Tyr Asp Pro
        35                  40                  45

Tyr Leu Asp Val Ala Leu Glu Ile Arg Gln Ala Ala Asn Ile Val Arg
    50                  55                  60

Ala Leu Glu Leu Phe Val Lys Ala Asp Val Leu Ser Gly Glu Asn Ala
65                  70                  75                  80
```

Tyr Met Cys Ala Lys Cys Lys Lys Lys Val Pro Ala Ser Lys Arg Phe
85 90 95

Thr Ile His Arg Thr Ser Asn Val Leu Thr Leu Ser Leu Lys Arg Phe
100 105 110

Ala Asn Phe Ser Gly Gly Lys Ile Thr Lys Asp Val Gly Tyr Pro Glu
115 120 125

Phe Leu Asn Ile Arg Pro Tyr Met Ser Gln Asn Asn Gly Asp Pro Val
130 135 140

Met Tyr Gly Leu Tyr Ala Val Leu Val His Ser Gly Tyr Ser Cys His
145 150 155 160

Ala Gly His Tyr Tyr Cys Tyr Val Lys Ala Ser Asn Gly Gln Trp Tyr
165 170 175

Gln Met Asn Asp Ser Leu Val His Ser Ser Asn Val Lys Val Val Leu
180 185 190

Asn Gln Gln Ala Tyr Val Leu Phe Tyr Leu Arg Ile Pro Gly Ser Lys
195 200 205

Lys Ser Pro Glu Gly Leu Ile Ser Arg Thr Gly Ser Ser Ser Leu Pro
210 215 220

Gly Arg Pro Ser Val Ile Pro Asp His Ser Lys Lys Asn Ile Gly Asn
225 230 235 240

Gly Ile Ile Ser Ser Pro Leu Thr Gly Lys Arg Gln Asp Ser Gly Thr
245 250 255

Met Lys Lys Pro His Thr Thr Glu Glu Ile Gly Val Pro Ile Ser Arg
260 265 270

Asn Gly Ser Thr Leu Gly Leu Lys Ser Gln Asn Gly Cys Ile Pro Pro
275 280 285

Lys Leu Pro Ser Gly Ser Pro Ser Pro Lys Leu Ser Gln Thr Pro Thr
290 295 300

His Met Pro Thr Ile Leu Asp Asp Pro Gly Lys Lys Val Lys Lys Pro
305 310 315 320

Ala Pro Pro Gln His Phe Ser Pro Arg Thr Ala Gln Gly Leu Pro Gly
325 330 335

Thr Ser Asn Ser Asn Ser Ser Arg Ser Gly Ser Gln Arg Gln Gly Ser
340 345 350

Trp Asp Ser Arg Asp Val Val Leu Ser Thr Ser Pro Lys Leu Leu Ala
355 360 365

Thr Ala Thr Ala Asn Gly His Gly Leu Lys Gly Asn Asp Glu Ser Ala
370 375 380

Gly Leu Asp Arg Arg Gly Ser Ser Ser Ser Ser Pro Glu His Ser Ala
385 390 395 400

Ser Ser Asp Ser Thr Lys Ala Pro Gln Thr Pro Arg Ser Gly Ala Ala
405 410 415

His Leu Cys Asp Ser Gln Glu Thr Asn Cys Ser Thr Ala Gly His Ser
420 425 430

Lys Thr Pro Pro Ser Gly Ala Asp Ser Lys Thr Val Lys Leu Lys Ser
435 440 445

Pro Val Leu Ser Asn Thr Thr Thr Glu Pro Ala Ser Thr Met Ser Pro
450 455 460

Pro Pro Ala Lys Lys Leu Ala Leu Ser Ala Lys Lys Ala Ser Thr Leu
465 470 475 480

Trp Arg Ala Thr Gly Asn Asp Leu Arg Pro Pro Pro Pro Ser Pro Ser
485 490 495

Ser Asp Leu Thr His Pro Met Lys Thr Ser His Pro Val Val Ala Ser
500 505 510

Thr Trp Pro Val His Arg Ala Arg Ala Val Ser Pro Ala Pro Gln Ser
515 520 525

Ser Ser Arg Leu Gln Pro Pro Phe Ser Pro His Pro Thr Leu Leu Ser
530 535 540

Ser Thr Pro Lys Pro Pro Gly Thr Ser Glu Pro Arg Ser Cys Ser Ser
545 550 555 560

Ile Ser Thr Ala Leu Pro Gln Val Asn Glu Asp Leu Val Ser Leu Pro
565 570 575

His Gln Leu Pro Glu Ala Ser Glu Pro Pro Gln Ser Pro Ser Glu Lys
580 585 590

Arg Lys Lys Thr Phe Val Gly Glu Pro Gln Arg Leu Gly Ser Glu Thr
595 600 605

Arg Leu Pro Gln His Ile Arg Glu Ala Thr Ala Ala Pro His Gly Lys
610 615 620

Arg Lys Arg Lys Lys Lys Lys Arg Pro Glu Asp Thr Ala Ala Ser Ala
625 630 635 640

Leu Gln Glu Gly Gln Thr Gln Arg Gln Pro Gly Ser Pro Met Tyr Arg
645 650 655

Arg Glu Gly Gln Ala Gln Leu Pro Ala Val Arg Arg Gln Glu Asp Gly
660 665 670

Thr Gln Pro Gln Val Asn Gly Gln Gln Val Gly Cys Val Thr Asp Gly
675 680 685

His His Ala Ser Ser Arg Lys Arg Arg Arg Lys Gly Ala Glu Gly Leu
690 695 700

Gly Glu Glu Gly Gly Leu His Gln Asp Pro Leu Arg His Ser Cys Ser
705 710 715 720

Pro Met Gly Asp Gly Asp Pro Glu Ala Met Glu Glu Ser Pro Arg Lys
725 730 735

Lys Lys Lys Lys Lys Asn Ser Arg Gly Gly Pro Val
740 745

<210> 39
<211> 526
<212> PRT
<213> Unknown

<220>
<223> Description of Unknown Organism:primate

<400> 39
Met Val Val Ala Leu Ser Phe Pro Glu Ala Asp Pro Ala Leu Ser Ser
1 5 10 15

Pro Asp Ala Pro Glu Leu His Gln Asp Glu Ala Gln Val Val Glu Glu
20 25 30

Leu Thr Val Asn Gly Lys His Ser Leu Ser Trp Glu Ser Pro Gln Gly
35 40 45

Pro Gly Cys Gly Leu Gln Asn Thr Gly Asn Ser Cys Tyr Leu Asn Ala
50 55 60

Ala Leu Gln Cys Leu Thr His Thr Pro Pro Leu Ala Asp Tyr Met Leu
65 70 75 80

Ser Gln Glu His Ser Gln Thr Cys Cys Ser Pro Glu Gly Cys Lys Leu
85 90 95

Cys Ala Met Glu Ala Leu Val Thr Gln Ser Leu Leu His Ser His Ser
100 105 110

Gly Asp Val Met Lys Pro Ser His Ile Leu Thr Ser Ala Phe His Lys
115 120 125

His Gln Gln Glu Asp Ala His Glu Phe Leu Met Phe Thr Leu Glu Thr
130 135 140

Met His Glu Ser Cys Leu Gln Val His Arg Gln Ser Lys Pro Thr Ser
145 150 155 160

Glu Asp Ser Ser Pro Ile His Asp Ile Phe Gly Gly Trp Trp Arg Ser
165 170 175

Gln Ile Lys Cys Leu Leu Cys Gln Gly Thr Ser Asp Thr Tyr Asp Arg
180 185 190

Phe Leu Asp Ile Pro Leu Asp Ile Ser Ser Ala Gln Ser Val Lys Gln
195 200 205

Ala Leu Trp Asp Thr Glu Lys Ser Glu Glu Leu Cys Gly Asp Asn Ala
210 215 220

Tyr Tyr Cys Gly Lys Cys Arg Gln Lys Met Pro Ala Ser Lys Thr Leu
225 230 235 240

```
His Val His Ile Ala Pro Lys Val Leu Met Val Val Leu Asn Arg Phe
                245                 250                 255

Ser Ala Phe Thr Gly Asn Lys Leu Asp Arg Lys Val Ser Tyr Pro Glu
            260                 265                 270

Phe Leu Asp Leu Lys Pro Tyr Leu Ser Glu Pro Thr Gly Gly Pro Leu
        275                 280                 285

Pro Tyr Ala Leu Tyr Ala Val Leu Val His Asp Gly Ala Thr Ser His
    290                 295                 300

Ser Gly His Tyr Phe Cys Cys Val Lys Ala Gly His Gly Lys Trp Tyr
305                 310                 315                 320

Lys Met Asp Asp Thr Lys Val Thr Arg Cys Asp Val Thr Ser Val Leu
                325                 330                 335

Asn Glu Asn Ala Tyr Val Leu Phe Tyr Val Gln Gln Ala Asn Leu Lys
            340                 345                 350

Gln Val Ser Ile Asp Met Pro Glu Gly Arg Ile Asn Glu Val Leu Asp
        355                 360                 365

Pro Glu Tyr Gln Leu Lys Lys Ser Arg Arg Lys Lys His Lys Lys Lys
    370                 375                 380

Ser Pro Phe Thr Glu Asp Leu Gly Glu Pro Cys Glu Asn Arg Asp Lys
385                 390                 395                 400

Arg Ala Ile Lys Glu Thr Ser Leu Gly Lys Gly Lys Val Leu Gln Glu
                405                 410                 415

Val Asn His Lys Lys Ala Gly Gln Lys His Gly Asn Thr Lys Leu Met
            420                 425                 430

Pro Gln Lys Gln Asn His Gln Lys Ala Gly Gln Asn Leu Arg Asn Thr
        435                 440                 445

Glu Val Glu Leu Asp Leu Pro Ala Asp Ala Ile Val Ile His Gln Pro
    450                 455                 460

Arg Ser Thr Ala Asn Trp Gly Arg Asp Ser Pro Asp Lys Glu Asn Gln
465                 470                 475                 480

Pro Leu His Asn Ala Asp Arg Leu Leu Thr Ser Gln Gly Pro Val Asn
                485                 490                 495

Thr Trp Gln Leu Cys Arg Gln Glu Gly Arg Arg Arg Ser Lys Lys Gly
            500                 505                 510

Gln Asn Lys Asn Lys Gln Gly Gln Arg Leu Leu Leu Val Cys
        515                 520                 525


<210> 40
<211> 545
<212> PRT
<213> Unknown

<220>
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<223> Description of Unknown Organism:primate

<400> 40

```
Met Val Val Ser Leu Ser Phe Pro Glu Ala Asp Pro Ala Leu Ser Ser
 1               5                  10                  15

Pro Gly Ala Gln Gln Leu His Gln Asp Glu Ala Gln Val Val Val Glu
            20                  25                  30

Leu Thr Ala Asn Asp Lys Pro Ser Leu Ser Trp Glu Cys Pro Gln Gly
        35                  40                  45

Pro Gly Cys Gly Leu Gln Asn Thr Gly Asn Ser Cys Tyr Leu Asn Ala
    50                  55                  60

Ala Leu Gln Cys Leu Thr His Thr Pro Pro Leu Ala Asp Tyr Met Leu
65                  70                  75                  80

Ser Gln Glu Tyr Ser Gln Thr Cys Cys Ser Pro Glu Gly Cys Lys Met
                85                  90                  95

Cys Ala Met Glu Ala His Val Thr Gln Ser Leu Leu His Ser His Ser
            100                 105                 110

Gly Asp Val Met Lys Pro Ser Gln Ile Leu Thr Ser Ala Phe His Lys
        115                 120                 125

His Gln Gln Glu Asp Ala His Glu Phe Leu Met Phe Thr Leu Glu Thr
    130                 135                 140

Met His Glu Ser Cys Leu Gln Val His Arg Gln Ser Glu Pro Thr Ser
145                 150                 155                 160

Glu Asp Ser Ser Pro Ile His Asp Ile Phe Gly Gly Leu Trp Arg Ser
                165                 170                 175

Gln Ile Lys Cys Leu His Cys Gln Gly Thr Ser Asp Thr Tyr Asp Arg
            180                 185                 190

Phe Leu Asp Val Pro Leu Asp Ile Ser Ser Ala Gln Ser Val Asn Gln
        195                 200                 205

Ala Leu Trp Asp Thr Glu Lys Ser Glu Glu Leu Arg Gly Glu Asn Ala
    210                 215                 220

Tyr Tyr Cys Gly Arg Cys Arg Gln Lys Met Pro Ala Ser Lys Thr Leu
225                 230                 235                 240

His Ile His Ser Ala Pro Lys Val Leu Leu Leu Val Leu Lys Arg Phe
                245                 250                 255

Ser Ala Phe Met Gly Asn Lys Leu Asp Arg Lys Val Ser Tyr Pro Glu
            260                 265                 270

Phe Leu Asp Leu Lys Pro Tyr Leu Ser Gln Pro Thr Gly Gly Pro Leu
        275                 280                 285

Pro Tyr Ala Leu Tyr Ala Val Leu Val His Glu Gly Ala Thr Cys His
    290                 295                 300
```

Ser Gly His Tyr Phe Ser Tyr Val Lys Ala Arg His Gly Ala Trp Tyr
305 310 315 320

Lys Met Asp Asp Thr Lys Val Thr Ser Cys Asp Val Thr Ser Val Leu
325 330 335

Asn Glu Asn Ala Tyr Val Leu Phe Tyr Val Gln Gln Thr Asp Leu Lys
340 345 350

Gln Val Ser Ile Asp Met Pro Glu Gly Arg Val His Glu Val Leu Asp
355 360 365

Pro Glu Tyr Gln Leu Lys Lys Ser Arg Arg Lys Lys His Lys Lys Lys
370 375 380

Ser Pro Cys Thr Glu Asp Ala Gly Glu Pro Cys Lys Asn Arg Glu Lys
385 390 395 400

Arg Ala Thr Lys Glu Thr Ser Leu Gly Glu Gly Lys Val Xaa Gln Glu
405 410 415

Lys Asn His Lys Lys Ala Gly Gln Lys His Glu Asn Thr Lys Leu Val
420 425 430

Pro Gln Glu Gln Asn His Gln Lys Leu Gly Gln Lys His Arg Ile Asn
435 440 445

Glu Ile Leu Pro Gln Glu Gln Asn His Gln Lys Ala Gly Gln Ser Leu
450 455 460

Arg Asn Thr Glu Gly Glu Leu Asp Leu Pro Ala Asp Ala Ile Val Ile
465 470 475 480

His Leu Leu Arg Ser Thr Glu Asn Trp Gly Arg Asp Ala Pro Asp Lys
485 490 495

Glu Asn Gln Pro Trp His Asn Ala Asp Arg Leu Leu Thr Ser Gln Asp
500 505 510

Pro Val Asn Thr Gly Gln Leu Cys Arg Gln Glu Gly Arg Arg Arg Ser
515 520 525

Lys Lys Gly Lys Asn Lys Asn Lys Gln Gly Gln Arg Leu Leu Leu Val
530 535 540

Cys
545

<210> 41
<211> 890
<212> DNA
<213> Unknown

<220>
<223> Description of Unknown Organism:primate

<220>
<221> CDS
<222> (15)..(500)

<220>
<221> misc_feature
<222> (53)
<223> nucleotide may be A or C

<220>
<221> misc_feature
<222> (123)
<223> nucleotide may be C or G

<220>
<221> misc_feature
<222> (124)
<223> nucleotide may be G or T

<220>
<221> misc_feature
<222> (125)
<223> nucleotide may be C or T

<220>
<221> misc_feature
<222> (525)
<223> nucleotide may be A, C, G, or T

<220>
<221> misc_feature
<222> (547)
<223> nucleotide may be A, C, G, or T

<220>
<221> misc_feature
<222> (835)
<223> nucleotide may be A, C, G, or T

<400> 41

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ggcacgagcc cacc atg aag ggt ttc aca gcc act ctc ttc ctc tgg act   50
                  Met Lys Gly Phe Thr Ala Thr Leu Phe Leu Trp Thr
                    1               5                  10

ctc att ttt ccc agc tgc agt gga ggc ggc ggt ggg aaa gcc tgg ccc   98
Leu Ile Phe Pro Ser Cys Ser Gly Gly Gly Gly Gly Lys Ala Trp Pro
         15                  20                  25

aca cac gtg gtc tgt agc gac agc cgc ttg gaa gtg ctc tac cag agt   146
Thr His Val Val Cys Ser Asp Ser Arg Leu Glu Val Leu Tyr Gln Ser
     30                  35                  40

tgc gat cca tta caa gat ttt ggc ttt tct gtt gaa aag tgt tcc aag   194
Cys Asp Pro Leu Gln Asp Phe Gly Phe Ser Val Glu Lys Cys Ser Lys
 45                  50                  55                  60

caa tta aaa tca aat atc aac att aga ttt gga att att ctg aga gag   242
Gln Leu Lys Ser Asn Ile Asn Ile Arg Phe Gly Ile Ile Leu Arg Glu
                 65                  70                  75

gac atc aaa gag ctt ttt ctt gac cta gct ctc atg tct caa ggc tca   290
Asp Ile Lys Glu Leu Phe Leu Asp Leu Ala Leu Met Ser Gln Gly Ser
             80                  85                  90
```

tct gtt ttg aat ttc tcc tat ccc atc tgt gag gcg gct ctg ccc aag 338
Ser Val Leu Asn Phe Ser Tyr Pro Ile Cys Glu Ala Ala Leu Pro Lys
95 100 105

ttt tct ttc tgt gga aga agg aaa gga gag cag att tac tat gct ggg 386
Phe Ser Phe Cys Gly Arg Arg Lys Gly Glu Gln Ile Tyr Tyr Ala Gly
110 115 120

cct gtc aat aat cct gaa ttt act att cct cag gga gaa tac cag gtt 434
Pro Val Asn Asn Pro Glu Phe Thr Ile Pro Gln Gly Glu Tyr Gln Val
125 130 135 140

ttg ctg gaa ctg tac act gaa aaa cgg tcc acc gtg gcc tgt gcc aat 482
Leu Leu Glu Leu Tyr Thr Glu Lys Arg Ser Thr Val Ala Cys Ala Asn
145 150 155

gct act atc atg tgc tcc tgactgtggg cctgttagca aaaactcaca 530
Ala Thr Ile Met Cys Ser
160

gccagctgca tctcgtcggg aaccttccaa gctcctctga ctgaacctac tgtgggagga 590

gaagcagctg atgacagaga gaggctctac aaagaagcgc ccccaaagag tgcagctgct 650

aattttagtc ccaggaccag acatccccag actccacaga tgtaatgaag tccccgaatg 710

tatctgtttc taaggagcct cttggcagtc cttaagcagt cttgagggtc catccttttt 770

ctctaattgg tcgcctccca ccagactcac ctgcttttca acttttagg agtgcttcct 830

cacacgttac caataataaa gaaagctggc caccaaaaaa aaaaaaaaaa aaaaaaaaaa 890

<210> 42
<211> 162
<212> PRT
<213> Unknown

<400> 42
Met Lys Gly Phe Thr Ala Thr Leu Phe Leu Trp Thr Leu Ile Phe Pro
1 5 10 15

Ser Cys Ser Gly Gly Gly Gly Gly Lys Ala Trp Pro Thr His Val Val
20 25 30

Cys Ser Asp Ser Arg Leu Glu Val Leu Tyr Gln Ser Cys Asp Pro Leu
35 40 45

Gln Asp Phe Gly Phe Ser Val Glu Lys Cys Ser Lys Gln Leu Lys Ser
50 55 60

Asn Ile Asn Ile Arg Phe Gly Ile Ile Leu Arg Glu Asp Ile Lys Glu
65 70 75 80

Leu Phe Leu Asp Leu Ala Leu Met Ser Gln Gly Ser Ser Val Leu Asn
85 90 95

Phe Ser Tyr Pro Ile Cys Glu Ala Ala Leu Pro Lys Phe Ser Phe Cys
100 105 110

Gly Arg Arg Lys Gly Glu Gln Ile Tyr Tyr Ala Gly Pro Val Asn Asn
115 120 125

Pro Glu Phe Thr Ile Pro Gln Gly Glu Tyr Gln Val Leu Leu Glu Leu
130 135 140

Tyr Thr Glu Lys Arg Ser Thr Val Ala Cys Ala Asn Ala Thr Ile Met
145 150 155 160

Cys Ser

<210> 43
<211> 486
<212> DNA
<213> Unknown

<220>
<223> Description of Unknown Organism:primate

<220>
<221> CDS
<222> (1)..(132)

<400> 43
ccc ctg ttt tct tcc ata ttt act gaa gct cag aag cag tat tgg gtc 48
Pro Leu Phe Ser Ser Ile Phe Thr Glu Ala Gln Lys Gln Tyr Trp Val
1 5 10 15

tgc aac tca tcc gat gca agt att tca tac acc tac tgt gat aaa atg 96
Cys Asn Ser Ser Asp Ala Ser Ile Ser Tyr Thr Tyr Cys Asp Lys Met
20 25 30

caa tac cca att tca att aat gtt aac ccc tgt ata gaattgaaag 142
Gln Tyr Pro Ile Ser Ile Asn Val Asn Pro Cys Ile
35 40

gatccaaagg attattgcac attttctaca ttccaaggag agatttaaag caattatatt 202

tcaatctcta tataactgtc aacaccatga atcttccaaa gcgcaaagaa gttatttgcc 262

gaggatctga tgacgattac tctttttgca gagctctgaa gggagagact gtgaatacaa 322

caatatcatt ctccttcaag ggaataaaat tttctaaggg aaaatacaaa tgtgttgttg 382

aagctatttc tgggagccca gaagaaatgc tcttttgctt ggagtttgtc atcctacacc 442

aacctaattc aaattagaat aaattgagta tttaaaaaaa aaaa 486

<210> 44
<211> 44
<212> PRT
<213> Unknown

<400> 44
Pro Leu Phe Ser Ser Ile Phe Thr Glu Ala Gln Lys Gln Tyr Trp Val
1 5 10 15

```
Cys Asn Ser Ser Asp Ala Ser Ile Ser Tyr Thr Tyr Cys Asp Lys Met
            20                  25                  30

Gln Tyr Pro Ile Ser Ile Asn Val Asn Pro Cys Ile
        35                  40
```

<210> 45
<211> 483
<212> DNA
<213> Unknown

<220>
<223> Description of Unknown Organism:primate

<220>
<221> CDS
<222> (1)..(480)

<400> 45

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atg ttc cca ttt ctg ttt ttt tcc acc ctg ttt tct tcc ata ttt act   48
Met Phe Pro Phe Leu Phe Phe Ser Thr Leu Phe Ser Ser Ile Phe Thr
  1               5                  10                  15

gaa gct cag aag cag tat tgg gtc tgc aac tca tcc gat gca agt att   96
Glu Ala Gln Lys Gln Tyr Trp Val Cys Asn Ser Ser Asp Ala Ser Ile
            20                  25                  30

tca tac acc tac tgt gat aaa atg caa tac cca att tca att aat gtt   144
Ser Tyr Thr Tyr Cys Asp Lys Met Gln Tyr Pro Ile Ser Ile Asn Val
        35                  40                  45

aac ccc tgt ata gaa ttg aaa gga tcc aaa gga tta ttg cac att ttc   192
Asn Pro Cys Ile Glu Leu Lys Gly Ser Lys Gly Leu Leu His Ile Phe
    50                  55                  60

tac att cca agg aga gat tta aag caa tta tat ttc aat ctc tat ata   240
Tyr Ile Pro Arg Arg Asp Leu Lys Gln Leu Tyr Phe Asn Leu Tyr Ile
65                  70                  75                  80

act gtc aac acc atg aat ctt cca aag cgc aaa gaa gtt att tgc cga   288
Thr Val Asn Thr Met Asn Leu Pro Lys Arg Lys Glu Val Ile Cys Arg
                85                  90                  95

gga tct gat gac gat tac tct ttt tgc aga gct ctg aag gga gag act   336
Gly Ser Asp Asp Asp Tyr Ser Phe Cys Arg Ala Leu Lys Gly Glu Thr
            100                 105                 110

gtg aat aca aca ata tca ttc tcc ttc aag gga ata aaa ttt tct aag   384
Val Asn Thr Thr Ile Ser Phe Ser Phe Lys Gly Ile Lys Phe Ser Lys
        115                 120                 125

gga aaa tac aaa tgt gtt gtt gaa gct att tct ggg agc cca gaa gaa   432
Gly Lys Tyr Lys Cys Val Val Glu Ala Ile Ser Gly Ser Pro Glu Glu
    130                 135                 140

atg ctc ttt tgc ttg gag ttt gtc atc cta cac caa cct aat tca aat   480
Met Leu Phe Cys Leu Glu Phe Val Ile Leu His Gln Pro Asn Ser Asn
145                 150                 155                 160

tag                                                             483
```

<210> 46
<211> 160
<212> PRT
<213> Unknown

<400> 46

```
Met Phe Pro Phe Leu Phe Phe Ser Thr Leu Phe Ser Ser Ile Phe Thr
  1               5                  10                  15

Glu Ala Gln Lys Gln Tyr Trp Val Cys Asn Ser Ser Asp Ala Ser Ile
             20                  25                  30

Ser Tyr Thr Tyr Cys Asp Lys Met Gln Tyr Pro Ile Ser Ile Asn Val
         35                  40                  45

Asn Pro Cys Ile Glu Leu Lys Gly Ser Lys Gly Leu Leu His Ile Phe
     50                  55                  60

Tyr Ile Pro Arg Arg Asp Leu Lys Gln Leu Tyr Phe Asn Leu Tyr Ile
 65                  70                  75                  80

Thr Val Asn Thr Met Asn Leu Pro Lys Arg Lys Glu Val Ile Cys Arg
                 85                  90                  95

Gly Ser Asp Asp Asp Tyr Ser Phe Cys Arg Ala Leu Lys Gly Glu Thr
            100                 105                 110

Val Asn Thr Thr Ile Ser Phe Ser Phe Lys Gly Ile Lys Phe Ser Lys
        115                 120                 125

Gly Lys Tyr Lys Cys Val Val Glu Ala Ile Ser Gly Ser Pro Glu Glu
    130                 135                 140

Met Leu Phe Cys Leu Glu Phe Val Ile Leu His Gln Pro Asn Ser Asn
145                 150                 155                 160
```

<210> 47
<211> 498
<212> DNA
<213> Unknown

<220>
<223> Description of Unknown Organism:rodent

<220>
<221> CDS
<222> (53)..(394)

<400> 47

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gtcgagtccg atggtcttcc tggcgagttt aaagtatcgg agatattaaa tc atg ttg 58
                                                          Met Leu
                                                            1

cca ttt att ctc ttt tcg acg ctg ctt tct ccc ata ttg act gaa tct   106
Pro Phe Ile Leu Phe Ser Thr Leu Leu Ser Pro Ile Leu Thr Glu Ser
          5                  10                  15

gag aag caa cag tgg ttc tgc aac tcc tcc gat gca att att tcc tac   154
```

```
Glu Lys Gln Gln Trp Phe Cys Asn Ser Ser Asp Ala Ile Ile Ser Tyr
 20                  25                  30

agt tat tgt gat cac ttg aaa ttc cct att tca att agt tct gaa ccc   202
Ser Tyr Cys Asp His Leu Lys Phe Pro Ile Ser Ile Ser Ser Glu Pro
 35                  40                  45                  50

tgc ata aga ctg agg gga acc aat gga ttt gtg cat gtt gag ttc att   250
Cys Ile Arg Leu Arg Gly Thr Asn Gly Phe Val His Val Glu Phe Ile
                 55                  60                  65

cca aga gga aac tta aaa tat tta tat ttc aac cta ttc atc agt gtc   298
Pro Arg Gly Asn Leu Lys Tyr Leu Tyr Phe Asn Leu Phe Ile Ser Val
             70                  75                  80

aac tcc ata gag ttg ccg aag cgt aag gaa gtt ctg tgc cat gga cat   346
Asn Ser Ile Glu Leu Pro Lys Arg Lys Glu Val Leu Cys His Gly His
         85                  90                  95

gat gat gac tat tct ttt tgc aga gct ctg aaa gga gga tat gct att   394
Asp Asp Asp Tyr Ser Phe Cys Arg Ala Leu Lys Gly Gly Tyr Ala Ile
    100                 105                 110

tagaaaatat gagactgtga atacatcaat accattctct ttcgagggaa tactatttcc 454

taagggccat tacagatgtg ttgcagaagc tattgctggg gata                  498
```

<210> 48
<211> 114
<212> PRT
<213> Unknown

<400> 48

```
Met Leu Pro Phe Ile Leu Phe Ser Thr Leu Leu Ser Pro Ile Leu Thr
 1               5                  10                  15

Glu Ser Glu Lys Gln Gln Trp Phe Cys Asn Ser Ser Asp Ala Ile Ile
            20                  25                  30

Ser Tyr Ser Tyr Cys Asp His Leu Lys Phe Pro Ile Ser Ile Ser Ser
        35                  40                  45

Glu Pro Cys Ile Arg Leu Arg Gly Thr Asn Gly Phe Val His Val Glu
    50                  55                  60

Phe Ile Pro Arg Gly Asn Leu Lys Tyr Leu Tyr Phe Asn Leu Phe Ile
65                  70                  75                  80

Ser Val Asn Ser Ile Glu Leu Pro Lys Arg Lys Glu Val Leu Cys His
                85                  90                  95

Gly His Asp Asp Asp Tyr Ser Phe Cys Arg Ala Leu Lys Gly Gly Tyr
            100                 105                 110

Ala Ile
```

<210> 49
<211> 141

<212> PRT
<213> Unknown

<220>
<223> Description of Unknown Organism:primate

<400> 49
Met Leu Pro Phe Ile Leu Phe Ser Thr Leu Leu Ser Pro Ile Leu Thr
1 5 10 15

Glu Ser Glu Lys Gln Gln Trp Phe Cys Asn Ser Ser Asp Ala Ile Ile
20 25 30

Ser Tyr Ser Tyr Cys Asp His Leu Lys Phe Pro Ile Ser Ile Ser Ser
35 40 45

Glu Pro Cys Ile Arg Leu Arg Gly Thr Asn Gly Phe Val His Val Glu
50 55 60

Phe Ile Pro Arg Gly Asn Leu Lys Tyr Leu Tyr Phe Asn Leu Phe Ile
65 70 75 80

Ser Val Asn Ser Ile Glu Leu Pro Lys Arg Lys Glu Val Leu Cys His
85 90 95

Gly His Asp Asp Asp Tyr Ser Phe Cys Arg Ala Leu Lys Gly Glu Thr
100 105 110

Val Asn Thr Ser Ile Pro Phe Ser Phe Glu Gly Ile Leu Phe Pro Lys
115 120 125

Gly His Tyr Arg Cys Val Ala Glu Ala Ile Ala Gly Asp
130 135 140

<210> 50
<211> 162
<212> PRT
<213> Unknown

<220>
<223> Description of Unknown Organism:rodent

<400> 50
Met Asn Gly Val Ala Ala Ala Leu Leu Val Trp Ile Leu Thr Ser Pro
1 5 10 15

Ser Ser Ser Asp His Gly Ser Glu Asn Gly Trp Pro Lys His Thr Ala
20 25 30

Cys Asn Ser Gly Gly Leu Glu Val Val Tyr Gln Ser Cys Asp Pro Leu
35 40 45

Gln Asp Phe Gly Leu Ser Ile Asp Gln Cys Ser Lys Gln Ile Gln Ser
50 55 60

Asn Leu Asn Ile Arg Phe Gly Ile Ile Leu Arg Gln Asp Ile Arg Lys
65 70 75 80

Leu Phe Leu Asp Ile Thr Leu Met Ala Lys Gly Ser Ser Ile Leu Asn
85 90 95

```
Tyr Ser Tyr Pro Leu Cys Glu Glu Asp Gln Pro Lys Phe Ser Phe Cys
            100                 105                 110

Gly Arg Arg Lys Gly Glu Gln Ile Tyr Tyr Ala Gly Pro Val Asn Asn
        115                 120                 125

Pro Gly Leu Asp Val Pro Gln Gly Glu Tyr Gln Leu Leu Leu Glu Leu
    130                 135                 140

Tyr Asn Glu Asn Arg Ala Thr Val Ala Cys Ala Asn Ala Thr Val Thr
145                 150                 155                 160

Ser Ser
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<210> 51
<211> 1158
<212> DNA
<213> Unknown

<220>
<223> Description of Unknown Organism:avian

<220>
<221> CDS
<222> (11)..(490)

<400> 51

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cggtgcaacc atg aag aca ttg aat gtt ctc gct ctc gtc tta gtc ctg    49
           Met Lys Thr Leu Asn Val Leu Ala Leu Val Leu Val Leu
             1               5                  10

ctt tgc atc aat gcc agc aca gag tgg cct aca cac aca gtc tgc aag   97
Leu Cys Ile Asn Ala Ser Thr Glu Trp Pro Thr His Thr Val Cys Lys
     15                  20                  25

gag gaa aac ttg gag ata tat tac aaa agc tgt gat ccc cag caa gac   145
Glu Glu Asn Leu Glu Ile Tyr Tyr Lys Ser Cys Asp Pro Gln Gln Asp
 30                  35                  40                  45

ttt gct ttc agc att gac cgt tgt tca gat gtc aca acc cac acc ttt   193
Phe Ala Phe Ser Ile Asp Arg Cys Ser Asp Val Thr Thr His Thr Phe
                 50                  55                  60

gac atc aga gct gca atg gtc cta aga caa agc atc aag gaa ctg tat   241
Asp Ile Arg Ala Ala Met Val Leu Arg Gln Ser Ile Lys Glu Leu Tyr
             65                  70                  75

gcc aag gtt gat ctg atc ata aat ggg aag act gtc tta agc tac tca   289
Ala Lys Val Asp Leu Ile Ile Asn Gly Lys Thr Val Leu Ser Tyr Ser
         80                  85                  90

gag aca ctc tgt gga cca ggc ctt tct aag cta att ttc tgt gga aag   337
Glu Thr Leu Cys Gly Pro Gly Leu Ser Lys Leu Ile Phe Cys Gly Lys
     95                  100                 105

aag aaa gga gaa cat ctc tac tat gag gga cca atc aca ctg gga atc   385
Lys Lys Gly Glu His Leu Tyr Tyr Glu Gly Pro Ile Thr Leu Gly Ile
110                 115                 120                 125
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aaa gaa atc cca cag cga gat tac act atc aca gca agg ctg act aac 433
Lys Glu Ile Pro Gln Arg Asp Tyr Thr Ile Thr Ala Arg Leu Thr Asn
130 135 140

gaa gat cgc gcc act gtt gct tgt gct gat ttt acc gtg aaa aat tat 481
Glu Asp Arg Ala Thr Val Ala Cys Ala Asp Phe Thr Val Lys Asn Tyr
145 150 155

tta gat tat taagcaaaac aacgcactcg gtccgactcc cttaaaacta 530
Leu Asp Tyr
160

cagattccta aaactattca agcccagtga gctgcttgca tgcttcagtg attctgaagg 590

aaagatctcc cgcacggtgg ttctgatgct gttcctcttc gtaattcaac ttttttggag 650

aagtcactag gccctaccct ctagtggtaa ttttatctcc aaatgcactc tgtagcccac 710

ttttcgcttt taatatatac agctgcaaat agaaagtatt tgataccaac attctcatct 770

caggatgaaa atagtacaaa gcagaagagg cgagagccaa aacagatttt tgcagtaagc 830

tatggaggta tccatttcta acacaagcta aagaagattg tcatatgtat tatgcagtta 890

tagcactcaa cattttcagt ttttcacaag gcctgtttgg agcctccatt ggtataaatt 950

ttgttgtaac cacagaacaa agaccaaata ggatgaacat ggctccatgt tcagtcactc 1010

tattcatatc atttaagttt tcatgattct tcttgtatat ttttttttat tctttaatgt 1070

ttacagtgat gtgagaatcc ttttgtttaa gctacatgct gttcccgctt gtcaataaat 1130

ctgcaagaaa aaaaaaaaaa aaaaaaaa 1158

<210> 52
<211> 160
<212> PRT
<213> Unknown

<400> 52
Met Lys Thr Leu Asn Val Leu Ala Leu Val Leu Val Leu Leu Cys Ile
1 5 10 15

Asn Ala Ser Thr Glu Trp Pro Thr His Thr Val Cys Lys Glu Glu Asn
20 25 30

Leu Glu Ile Tyr Tyr Lys Ser Cys Asp Pro Gln Gln Asp Phe Ala Phe
35 40 45

Ser Ile Asp Arg Cys Ser Asp Val Thr Thr His Thr Phe Asp Ile Arg
50 55 60

Ala Ala Met Val Leu Arg Gln Ser Ile Lys Glu Leu Tyr Ala Lys Val
65 70 75 80

Asp Leu Ile Ile Asn Gly Lys Thr Val Leu Ser Tyr Ser Glu Thr Leu
85 90 95

Cys Gly Pro Gly Leu Ser Lys Leu Ile Phe Cys Gly Lys Lys Lys Gly
100 105 110

Glu His Leu Tyr Tyr Glu Gly Pro Ile Thr Leu Gly Ile Lys Glu Ile
115 120 125

Pro Gln Arg Asp Tyr Thr Ile Thr Ala Arg Leu Thr Asn Glu Asp Arg
130 135 140

Ala Thr Val Ala Cys Ala Asp Phe Thr Val Lys Asn Tyr Leu Asp Tyr
145 150 155 160

<210> 53
<211> 2684
<212> DNA
<213> Unknown

<220>
<223> Description of Unknown Organism:primate

<220>
<221> CDS
<222> (45)..(1256)

<400> 53
gaattcggca cgagggcgag gttttataca cctgaaagaa gaga atg tca aga cga 56
Met Ser Arg Arg
1

agt agc cgt tta caa gct aag cag cag ccc cag ccc agc cag acg gaa 104
Ser Ser Arg Leu Gln Ala Lys Gln Gln Pro Gln Pro Ser Gln Thr Glu
5 10 15 20

tcc ccc caa gaa gcc cag ata atc cag gcc aag aag agg aaa act acc 152
Ser Pro Gln Glu Ala Gln Ile Ile Gln Ala Lys Lys Arg Lys Thr Thr
25 30 35

cag gat gtc aaa aaa aga aga gag gag gtc acc aag aaa cat cag tat 200
Gln Asp Val Lys Lys Arg Arg Glu Glu Val Thr Lys Lys His Gln Tyr
40 45 50

gaa att agg aat tgt tgg cca cct gta tta tct ggg ggg atc agt cct 248
Glu Ile Arg Asn Cys Trp Pro Pro Val Leu Ser Gly Gly Ile Ser Pro
55 60 65

tgc att atc att gaa aca cct cac aaa gaa ata gga aca agt gat ttc 296
Cys Ile Ile Ile Glu Thr Pro His Lys Glu Ile Gly Thr Ser Asp Phe
70 75 80

tcc aga ttt aca aat tac aga ttt aaa aat ctt ttt att aat cct tca 344
Ser Arg Phe Thr Asn Tyr Arg Phe Lys Asn Leu Phe Ile Asn Pro Ser
85 90 95 100

cct ttg cct gat tta agc tgg gga tgt tca aaa gaa gtc tgg cta aac 392
Pro Leu Pro Asp Leu Ser Trp Gly Cys Ser Lys Glu Val Trp Leu Asn
105 110 115

atg tta aaa aag gag agc aga tat gtt cat gac aaa cat ttt gaa gtt 440
Met Leu Lys Lys Glu Ser Arg Tyr Val His Asp Lys His Phe Glu Val
120 125 130

```
ctg cat tct gac ttg gaa cca cag atg agg tcc ata ctt cta gac tgg   488
Leu His Ser Asp Leu Glu Pro Gln Met Arg Ser Ile Leu Leu Asp Trp
        135                 140                 145

ctt tta gag gta tgt gaa gta tac aca ctt cat agg gaa aca ttt tat   536
Leu Leu Glu Val Cys Glu Val Tyr Thr Leu His Arg Glu Thr Phe Tyr
    150                 155                 160

ctt gca caa gac ttt ttt gat aga ttt atg ttg aca caa aag gat ata   584
Leu Ala Gln Asp Phe Phe Asp Arg Phe Met Leu Thr Gln Lys Asp Ile
165                 170                 175                 180

aat aaa aat atg ctt caa ctc att gga att acc tca tta ttc att gct   632
Asn Lys Asn Met Leu Gln Leu Ile Gly Ile Thr Ser Leu Phe Ile Ala
                185                 190                 195

tcc aaa ctt gag gaa atc tat gct cct aaa ctc caa gag ttt gct tac   680
Ser Lys Leu Glu Glu Ile Tyr Ala Pro Lys Leu Gln Glu Phe Ala Tyr
            200                 205                 210

gtc act gat ggt gct tgc agt gaa gaa gat atc tta agg atg gaa ctc   728
Val Thr Asp Gly Ala Cys Ser Glu Glu Asp Ile Leu Arg Met Glu Leu
        215                 220                 225

att ata tta aag gct tta aaa tgg gaa ctt tgt cct gta aca atc atc   776
Ile Ile Leu Lys Ala Leu Lys Trp Glu Leu Cys Pro Val Thr Ile Ile
    230                 235                 240

tcc tgg cta aat ctc ttt ctc caa gtt gat gct ctt aaa gat gct cct   824
Ser Trp Leu Asn Leu Phe Leu Gln Val Asp Ala Leu Lys Asp Ala Pro
245                 250                 255                 260

aaa gtt ctt cta cct cag tat tct cag gaa aca ttc att caa ata gct   872
Lys Val Leu Leu Pro Gln Tyr Ser Gln Glu Thr Phe Ile Gln Ile Ala
                265                 270                 275

cag ctt tta gat ctg tgt att cta gcc att gat tca tta gag ttc cag   920
Gln Leu Leu Asp Leu Cys Ile Leu Ala Ile Asp Ser Leu Glu Phe Gln
            280                 285                 290

tac aga ata ctg act gct gct gcc ttg tgc cat ttt acc tcc att gaa   968
Tyr Arg Ile Leu Thr Ala Ala Ala Leu Cys His Phe Thr Ser Ile Glu
        295                 300                 305

gtg gtt aag aaa gcc tca ggt ttg gag tgg gac agt att tca gaa tgt   1016
Val Val Lys Lys Ala Ser Gly Leu Glu Trp Asp Ser Ile Ser Glu Cys
    310                 315                 320

gta gat tgg atg gta cct ttt gtc aat gta gta aaa agt act agt cca   1064
Val Asp Trp Met Val Pro Phe Val Asn Val Val Lys Ser Thr Ser Pro
325                 330                 335                 340

gtg aag ctg aag act ttt aag aag att cct atg gaa gac aga cat aat   1112
Val Lys Leu Lys Thr Phe Lys Lys Ile Pro Met Glu Asp Arg His Asn
                345                 350                 355

atc cag aca cat aca aac tat ttg gct atg ctg gag gaa gta aat tac   1160
Ile Gln Thr His Thr Asn Tyr Leu Ala Met Leu Glu Glu Val Asn Tyr
            360                 365                 370
```

ata aac acc ttc aga aaa ggg gga cag ttg tca cca gtg tgc aat gga 1208
Ile Asn Thr Phe Arg Lys Gly Gly Gln Leu Ser Pro Val Cys Asn Gly
375 380 385

ggc att atg aca cca ccg aag agc act gaa aaa cca cca gga aaa cac 1256
Gly Ile Met Thr Pro Pro Lys Ser Thr Glu Lys Pro Pro Gly Lys His
390 395 400

taaagaagat aactaagcaa acaagttgga attcaccaag attgggtaga actggtatca 1316

ctgaactact aaagttttac agaaagtagt gctgtgattg attgccctag ccaattcaca 1376

agttacactg ccattctgat tttaaaactt acaattggca ctaaagaata catttaatta 1436

tttcctatgt tagctgttaa agaaacagca ggacttgttt acaaagatgt cttcattccc 1496

aaggttactg gatagaagcc aaccacagtc tataccatag caatgttttt cctttaatcc 1556

agtgttactg tgtttatctt gataaactag gaattttgtc actggagttt tggactggat 1616

aagtgctacc ttaaagggta tactaagtga tacagtactt tgaatctagt tgttagattc 1676

tcaaaattcc tacactcttg actagtgcaa tttggttctt gaaaattaaa tttaaacttg 1736

tttacaaagg tttagttttg taataaggtg actaatttat ctatagctgc tatagcaagc 1796

tattataaaa cttgaatttc tacaaatggt gaaatttaat gtttttaaa ctagtttatt 1856

tgccttgcca taacacattt tttaactaat aaggcttaga tgaacatggt gttcaacctg 1916

tgctctaaac agtgggagta ccaaagaaat tataaacaag ataaatgctg tggctccttc 1976

ctaactgggg ctttcttgac atgtaggttg cttggtaata acctttttgt atatcacaat 2036

ttgggtgaaa aacttaagta ccctttcaaa ctatttatat gaggaagtca ctttactact 2096

ctaagatatc cctaaggaat ttttttttt aatttagtgt gactaaggct ttatttatgt 2156

ttgtgaaact gttaaggtcc tttctaaatt cctccattgt gagataagga cagtgtcaaa 2216

gtgataaagc ttaacacttg acctaaactt ctattttctt aaggaagaag agtattaaat 2276

atatactgac tcctagaaat ctatttatta aaaaaagaca tgaaaacttg ctgtacatag 2336

gctagctatt tctaaatatt ttaaattagc ttttctaaaa aaaaaatcca gcctcataaa 2396

gtagattaga aaactagatt gctagtttat tttgttatca gatatgtgaa tctcttctcc 2456

ctttgaagaa actatacatt tattgttacg gtatgaagtc ttctgtatag tttgtttta 2516

aactaatatt tgtttcagta ttttgtctga aaagaaaaca ccactaattg tgtacatatg 2576

tattatataa acttaacctt ttaatactgt ttatttttag cccatgttta aaaaataaaa 2636

gttaaaaaaa tttaactgct aaaaaaaaaa aaaaaaaagt gcggccgc 2684

<210> 54
<211> 404
<212> PRT

<213> Unknown

<400> 54

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Met Ser Arg Arg Ser Ser Arg Leu Gln Ala Lys Gln Gln Pro Gln Pro
  1               5                  10                  15

Ser Gln Thr Glu Ser Pro Gln Glu Ala Gln Ile Ile Gln Ala Lys Lys
            20                  25                  30

Arg Lys Thr Thr Gln Asp Val Lys Lys Arg Arg Glu Glu Val Thr Lys
        35                  40                  45

Lys His Gln Tyr Glu Ile Arg Asn Cys Trp Pro Pro Val Leu Ser Gly
    50                  55                  60

Gly Ile Ser Pro Cys Ile Ile Ile Glu Thr Pro His Lys Glu Ile Gly
65                  70                  75                  80

Thr Ser Asp Phe Ser Arg Phe Thr Asn Tyr Arg Phe Lys Asn Leu Phe
                85                  90                  95

Ile Asn Pro Ser Pro Leu Pro Asp Leu Ser Trp Gly Cys Ser Lys Glu
            100                 105                 110

Val Trp Leu Asn Met Leu Lys Lys Glu Ser Arg Tyr Val His Asp Lys
        115                 120                 125

His Phe Glu Val Leu His Ser Asp Leu Glu Pro Gln Met Arg Ser Ile
    130                 135                 140

Leu Leu Asp Trp Leu Leu Glu Val Cys Glu Val Tyr Thr Leu His Arg
145                 150                 155                 160

Glu Thr Phe Tyr Leu Ala Gln Asp Phe Phe Asp Arg Phe Met Leu Thr
                165                 170                 175

Gln Lys Asp Ile Asn Lys Asn Met Leu Gln Leu Ile Gly Ile Thr Ser
            180                 185                 190

Leu Phe Ile Ala Ser Lys Leu Glu Glu Ile Tyr Ala Pro Lys Leu Gln
        195                 200                 205

Glu Phe Ala Tyr Val Thr Asp Gly Ala Cys Ser Glu Glu Asp Ile Leu
    210                 215                 220

Arg Met Glu Leu Ile Ile Leu Lys Ala Leu Lys Trp Glu Leu Cys Pro
225                 230                 235                 240

Val Thr Ile Ile Ser Trp Leu Asn Leu Phe Leu Gln Val Asp Ala Leu
                245                 250                 255

Lys Asp Ala Pro Lys Val Leu Leu Pro Gln Tyr Ser Gln Glu Thr Phe
            260                 265                 270

Ile Gln Ile Ala Gln Leu Leu Asp Leu Cys Ile Leu Ala Ile Asp Ser
        275                 280                 285

Leu Glu Phe Gln Tyr Arg Ile Leu Thr Ala Ala Ala Leu Cys His Phe
    290                 295                 300
```

```
Thr Ser Ile Glu Val Val Lys Lys Ala Ser Gly Leu Glu Trp Asp Ser
305                 310                 315                 320

Ile Ser Glu Cys Val Asp Trp Met Val Pro Phe Val Asn Val Val Lys
                325                 330                 335

Ser Thr Ser Pro Val Lys Leu Lys Thr Phe Lys Lys Ile Pro Met Glu
            340                 345                 350

Asp Arg His Asn Ile Gln Thr His Thr Asn Tyr Leu Ala Met Leu Glu
        355                 360                 365

Glu Val Asn Tyr Ile Asn Thr Phe Arg Lys Gly Gly Gln Leu Ser Pro
    370                 375                 380

Val Cys Asn Gly Gly Ile Met Thr Pro Pro Lys Ser Thr Glu Lys Pro
385                 390                 395                 400

Pro Gly Lys His
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<210> 55
<211> 1764
<212> DNA
<213> Unknown

<220>
<223> Description of Unknown Organism:primate

<220>
<221> CDS
<222> (26)..(1210)

<400> 55

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ccgggatgcg aaggagcggg acacc atg aag gag gac ggc ggc gcg gag ttc   52
                            Met Lys Glu Asp Gly Gly Ala Glu Phe
                              1               5

tcg gct cgc tcc agg aag agg aag gca aac gtg acc gtt ttt ttg cag   100
Ser Ala Arg Ser Arg Lys Arg Lys Ala Asn Val Thr Val Phe Leu Gln
 10                  15                  20                  25

gat cca gat gaa gaa atg gcc aaa atc gac agg acg gcg agg gac cag   148
Asp Pro Asp Glu Glu Met Ala Lys Ile Asp Arg Thr Ala Arg Asp Gln
                30                  35                  40

tgt ggg agc cag cct tgg gac aat aat gca gtc tgt gca gac ccc tgc   196
Cys Gly Ser Gln Pro Trp Asp Asn Asn Ala Val Cys Ala Asp Pro Cys
            45                  50                  55

tcc ctg atc ccc aca cct gac aaa gaa gat gat gac cgg gtt tac cca   244
Ser Leu Ile Pro Thr Pro Asp Lys Glu Asp Asp Asp Arg Val Tyr Pro
        60                  65                  70

aac tca acg tgc aag cct cgg att att gca cca tcc aga ggc tcc ccg   292
Asn Ser Thr Cys Lys Pro Arg Ile Ile Ala Pro Ser Arg Gly Ser Pro
    75                  80                  85

ctg cct gta ctg agc tgg gca aat aga gag gaa gtc tgg aaa atc atg   340
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```
Leu Pro Val Leu Ser Trp Ala Asn Arg Glu Glu Val Trp Lys Ile Met
 90                  95                 100                 105

tta aac aag gaa aag aca tac tta agg gat cag cac ttt ctt gag caa  388
Leu Asn Lys Glu Lys Thr Tyr Leu Arg Asp Gln His Phe Leu Glu Gln
                110                 115                 120

cac cct ctt ctg cag cca aaa atg cga gca att ctt ctg gat tgg tta  436
His Pro Leu Leu Gln Pro Lys Met Arg Ala Ile Leu Leu Asp Trp Leu
            125                 130                 135

atg gag gtg tgt gaa gtc tat aaa ctt cac agg gag acc ttt tac ttg  484
Met Glu Val Cys Glu Val Tyr Lys Leu His Arg Glu Thr Phe Tyr Leu
        140                 145                 150

gca caa gat ttc ttt gac cgg tat atg gcg aca caa gaa aat gtt gta  532
Ala Gln Asp Phe Phe Asp Arg Tyr Met Ala Thr Gln Glu Asn Val Val
    155                 160                 165

aaa act ctt tta cag ctt att ggg att tca tct tta ttt att gca gcc  580
Lys Thr Leu Leu Gln Leu Ile Gly Ile Ser Ser Leu Phe Ile Ala Ala
170                 175                 180                 185

aaa ctt gag gaa atc tat cct cca aag ttg cac cag ttt gcg tat gtg  628
Lys Leu Glu Glu Ile Tyr Pro Pro Lys Leu His Gln Phe Ala Tyr Val
                190                 195                 200

aca gat gga gct tgt tca gga gat gaa att ctc acc atg gaa tta atg  676
Thr Asp Gly Ala Cys Ser Gly Asp Glu Ile Leu Thr Met Glu Leu Met
            205                 210                 215

att atg aag gcc ctt aag tgg cgt tta agt ccc ctg act att gtg tcc  724
Ile Met Lys Ala Leu Lys Trp Arg Leu Ser Pro Leu Thr Ile Val Ser
        220                 225                 230

tgg ctg aat gta tac atg cag gtt gca tat cta aat gac tta cat gaa  772
Trp Leu Asn Val Tyr Met Gln Val Ala Tyr Leu Asn Asp Leu His Glu
    235                 240                 245

gtg cta ctg ccg cag tat ccc cag caa atc ttt ata cag att gca gag  820
Val Leu Leu Pro Gln Tyr Pro Gln Gln Ile Phe Ile Gln Ile Ala Glu
250                 255                 260                 265

ctg ttg gat ctc tgt gtc ctg gat gtt gac tgc ctt gaa ttt cct tat  868
Leu Leu Asp Leu Cys Val Leu Asp Val Asp Cys Leu Glu Phe Pro Tyr
                270                 275                 280

ggt ata ctt gct gct tcg gcc ttg tat cat ttc tcg tca tct gaa ttg  916
Gly Ile Leu Ala Ala Ser Ala Leu Tyr His Phe Ser Ser Ser Glu Leu
            285                 290                 295

atg caa aag gtt tca ggg tat cag tgg tgc gac ata gag aac tgt gtc  964
Met Gln Lys Val Ser Gly Tyr Gln Trp Cys Asp Ile Glu Asn Cys Val
        300                 305                 310

aag tgg atg gtt cca ttt gcc atg gtt ata agg gag acg ggg agc tca 1012
Lys Trp Met Val Pro Phe Ala Met Val Ile Arg Glu Thr Gly Ser Ser
    315                 320                 325

aaa ctg aag cac ttc agg ggc gtc gct gat gaa gat gca cac aac ata 1060
```

Lys Leu Lys His Phe Arg Gly Val Ala Asp Glu Asp Ala His Asn Ile
330 335 340 345

cag acc cac aga gac agc ttg gat ttg ctg gac aaa gcc cga gca aag 1108
Gln Thr His Arg Asp Ser Leu Asp Leu Leu Asp Lys Ala Arg Ala Lys
350 355 360

aaa gcc atg ttg tct gaa caa aat agg gct tct cct ctc ccc agt ggg 1156
Lys Ala Met Leu Ser Glu Gln Asn Arg Ala Ser Pro Leu Pro Ser Gly
365 370 375

ctc ctc acc ccg cca cag agc ggt aag aag cag agc agc ggg ccg gaa 1204
Leu Leu Thr Pro Pro Gln Ser Gly Lys Lys Gln Ser Ser Gly Pro Glu
380 385 390

atg gcg tgaccacccc atccttctcc accaaagaca gttgcgccgc tgctccacgt 1260
Met Ala
395

tctcttctgt ctgttgcagc ggaggcgtgc gtttgctttt acagatatct gaatggaaga 1320

gtgtttcttc cacaacagaa gtatttctgt ggatggcatc aaacagggca aagtgttttt 1380

tattgaatgc ttataggttt tttttaaata agtgggtcaa gtacaccagc cacctccaga 1440

caccagtgcg tgctcccgat gctgctatgg aaggtgctac ttgacctaag ggactcccac 1500

aacaacaaaa gcttgaagct gtggaggcgc acggtggcgt ggctctcctc gcaggtgttc 1560

tgggctccgt tgtaccaagt ggagcaggtg gttgcgggca agcgttgtgc agagcccata 1620

gccagctggg caggggggctg ccctctccac attatcagtt gacagtgtac aatgcctttg 1680

atgaactgtt ttgtaagtgc tgctatatct atccattttt taataaagct aatactgttt 1740

ctttagagca cactggcggg tcgt 1764

<210> 56
<211> 395
<212> PRT
<213> Unknown

<400> 56
Met Lys Glu Asp Gly Gly Ala Glu Phe Ser Ala Arg Ser Arg Lys Arg
1 5 10 15

Lys Ala Asn Val Thr Val Phe Leu Gln Asp Pro Asp Glu Glu Met Ala
20 25 30

Lys Ile Asp Arg Thr Ala Arg Asp Gln Cys Gly Ser Gln Pro Trp Asp
35 40 45

Asn Asn Ala Val Cys Ala Asp Pro Cys Ser Leu Ile Pro Thr Pro Asp
50 55 60

Lys Glu Asp Asp Asp Arg Val Tyr Pro Asn Ser Thr Cys Lys Pro Arg
65 70 75 80

Ile Ile Ala Pro Ser Arg Gly Ser Pro Leu Pro Val Leu Ser Trp Ala
85 90 95

Asn Arg Glu Glu Val Trp Lys Ile Met Leu Asn Lys Glu Lys Thr Tyr
100 105 110

Leu Arg Asp Gln His Phe Leu Glu Gln His Pro Leu Leu Gln Pro Lys
115 120 125

Met Arg Ala Ile Leu Leu Asp Trp Leu Met Glu Val Cys Glu Val Tyr
130 135 140

Lys Leu His Arg Glu Thr Phe Tyr Leu Ala Gln Asp Phe Phe Asp Arg
145 150 155 160

Tyr Met Ala Thr Gln Glu Asn Val Val Lys Thr Leu Leu Gln Leu Ile
165 170 175

Gly Ile Ser Ser Leu Phe Ile Ala Ala Lys Leu Glu Glu Ile Tyr Pro
180 185 190

Pro Lys Leu His Gln Phe Ala Tyr Val Thr Asp Gly Ala Cys Ser Gly
195 200 205

Asp Glu Ile Leu Thr Met Glu Leu Met Ile Met Lys Ala Leu Lys Trp
210 215 220

Arg Leu Ser Pro Leu Thr Ile Val Ser Trp Leu Asn Val Tyr Met Gln
225 230 235 240

Val Ala Tyr Leu Asn Asp Leu His Glu Val Leu Leu Pro Gln Tyr Pro
245 250 255

Gln Gln Ile Phe Ile Gln Ile Ala Glu Leu Leu Asp Leu Cys Val Leu
260 265 270

Asp Val Asp Cys Leu Glu Phe Pro Tyr Gly Ile Leu Ala Ala Ser Ala
275 280 285

Leu Tyr His Phe Ser Ser Ser Glu Leu Met Gln Lys Val Ser Gly Tyr
290 295 300

Gln Trp Cys Asp Ile Glu Asn Cys Val Lys Trp Met Val Pro Phe Ala
305 310 315 320

Met Val Ile Arg Glu Thr Gly Ser Ser Lys Leu Lys His Phe Arg Gly
325 330 335

Val Ala Asp Glu Asp Ala His Asn Ile Gln Thr His Arg Asp Ser Leu
340 345 350

Asp Leu Leu Asp Lys Ala Arg Ala Lys Lys Ala Met Leu Ser Glu Gln
355 360 365

Asn Arg Ala Ser Pro Leu Pro Ser Gly Leu Leu Thr Pro Pro Gln Ser
370 375 380

Gly Lys Lys Gln Ser Ser Gly Pro Glu Met Ala
385 390 395